ARTICLE

FERTILITY & REPRODUCTION

OPEN ACCESS

Clinical Outcomes of Oral vs. Transdermal Estrogen for Endometrial Preparation for Frozen Thawed Embryo Transfer in HRT-FET Cycles: A Systematic Review and Meta-Analysis

Peter Humaidan [1], Kshitiz Murdia [2], Vipin Chandra [2], Nihar Bhoi [2,*], Isha Suwalka [3], Ritu Punhani [4]

[1]Aarhus University, Aarhus, Denmark
[2]Department of Reproductive Medicine, Indira IVF Hospital Pvt Ltd, Udaipur 313001, Rajasthan, India
[3]Department of Research and Publication, Indira IVF Hospital Pvt Ltd, Udaipur 313001, Rajasthan, India
[4]Department of Reproductive Medicine, Indira IVF Hospital Pvt Ltd, Delhi, India

ABSTRACT

Background and Purpose: Among different routes of estrogen formulations, the transdermal route has obtained popularity in recent years for endometrial preparation in hormone replacement (HRT) frozen embryo transfer (FET) cycles. However, no clear evidence is available regarding clinical outcome of the transdermal route. This meta-analysis investigated the clinical outcomes of oral versus transdermal estrogen for endometrial preparation for FET in HRT-FET cycles.

Methods: A comprehensive literature search was performed for all published randomized controlled trials (RCTs) before May 30, 2022, in electronic databases, including PubMed, Cochrane Library, Embase, CINAHL, Trip Database, Worldwide Science, and Google Scholar. Outcomes, including endometrial thickness, implantation rate (IR), miscarriage rate (MR), clinical pregnancy rate (CPR), and live birth rate (LBR), were measured using pooled odds ratio (OR) or standardized mean difference (SMD) with 95% confidence intervals (CIs).

Results: Seven studies involving a total of 898 IVF patients were included in the meta-analysis. In a pooled analysis, endometrial thickness (ET) was more in the transdermal group as compared to the oral estrogen group (SMD = 0.16; 95% CI = 0.02–0.31). However, no significant association for IR (OR = 0.76; 95% CI = 0.42–1.38), CPR (OR = 0.98; 95% CI = 0.74–1.31), MR (OR = 1.28; 95% CI = 0.79–2.06), and LBR (OR = 0.73; 95% CI = 0.43–1.23) was found between oral versus transdermal estrogen groups.

Conclusions: In HRT-FET cycles using oral or transdermal estrogen, no significant difference was seen in clinical outcomes of IR, CPR, and LBR rates; however, a trend for a higher endometrial thickness was noted in the transdermal group.

***Keywords*:** Estrogen Oral; Transdermal Estrogen Gel; Embryo Transfer, Priming of the Endometrium; Frozen Embryo Transfer; Estradiol; Pregnancy Rate; Live Birth Rate.

"सार"

[ABSTRACT IN HINDI]

पृष्ठभूमि और उद्देश्य: हाल के वर्षों में एस्ट्रोजेन फॉर्मूलेशन के अलग-अलग रूट्स में ट्रांसडर्मल रूट हार्मोन रिप्लेसमेंट थेरेपी (एचआरटी) - फ्रोज़न-थॉ एम्ब्रियो ट्रांसफर (एफईटी) साइकल्स में एंडोमेट्रियल प्रिपरेशन के क्षेत्र में खासे लोकप्रिय हुए हैं । हालाँकि, ट्रांसडर्मल मार्ग के क्लिनिकल आउटकम के बारे में कोई स्पष्ट प्रमाण उपलब्ध नहीं है। इस मेटा-विश्लेषण ने एचआरटी-एफईटी साइकल्स में फ्रोज़न-थॉ एम्ब्रियो ट्रांसफर के लिए एंडोमेट्रियल प्रिपरेशन के लिए ओरल वर्सेज ट्रांसडर्मल एस्ट्रोजन के क्लिनिकल आउटकम की जांच की।

Received 8 June 2023; Accepted 28 March 2024; Published 6 July 2024

*Correspondence should be addressed to: Dr. Nihar Bhoi, Department of Reproductive Medicine, Indira IVF Hospital Private Limited 44, Amar Niwas kumharo ka Bhatta, Udaipur-313001 Rajasthan, India. Email: drniharbhoi@gmail.com

पद्धति: पबमेड, कोक्रेन लाइब्रेरी, एम्बेस, सीआईएनएएचएल, ट्रिप डेटाबेस, वर्ल्डवाइड साइंस और गूगल स्कॉलर सहित इलेक्ट्रॉनिक डेटाबेस में 30 मई, 2022 से पहले सभी प्रकाशित रैंडमाईज कंट्रोल्ड ट्रायल्स (आरसीटी) के लिए एक व्यापक लिटरेचर सर्च की गई थी। एंडोमेट्रियल थिकनेस, प्रत्यारोपण दर (आईआर), गर्भपात दर (एमआर), नैदानिक गर्भावस्था दर (सीपीआर), और जीवित जन्म दर (एलबीआर) आदि परिणामों को पूल्ड ऑड्स रेशो (ओआर) या 95% कांफिडेंस इंटरवल (सीआई) का उपयोग कर स्टैण्डर्डाइज मीन डिफ़रेंस (एसएमडी) के द्वारा मापा गया।

परिणाम: मेटा-विश्लेषण में सात अध्ययनों कुल 898 इन-विट्रो फर्टिलाइजेशन (आईवीएफ) रोगी शामिल थे। पूल्ड विश्लेषण में, ओरल एस्ट्रोजन ग्रुप (एसएमडी = 0.16; 95% सीआई = 0.02-0.31) की तुलना में ट्रांसडर्मल समूह में एंडोमेट्रियल थिकनेस (ईटी) अधिक पाई गई । लेकिन आईआर (ओआर = 0.76; 95% सीआई = 0.42-1.38), सीपीआर (ओआर = 0.98; 95% सीआई = 0.74-1.31), एमआर (ओआर = 1.28; 95% सीआई = 0.79-2.06), और एलबीआर (ओआर = 0.73; 95% सीआई = 0.43-1.23) ओरल वर्सेज ट्रांसडर्मल एस्ट्रोजन ग्रुप्स के बीच कोई विशेष सहसंबंध नहीं पाया गया। ।

निष्कर्ष: ओरल या ट्रांसडर्मल एस्ट्रोजन का उपयोग करने पर एचआरटी-एफईटी साइकल्स में, आईआर, सीपीआर और एलबीआर दरों के संदर्भ में क्लिनिकल आउटकम में कोई महत्वपूर्ण अंतर नहीं देखा गया; हालाँकि, ट्रांसडर्मल समूह में एंडोमेट्रियल मोटाई अधिक पाई गई ।

कीवर्ड: एस्ट्रोजन ओरल; ट्रांसडर्मल एस्ट्रोजन जेल; एम्ब्रियो ट्रांसफर, एंडोमेट्रियम का प्राइमिंग; फ्रोजन एम्ब्रियो ट्रांसफर; एस्ट्राडियोल; प्रेगनेंसी रेट; एलबीआर.

INTRODUCTION

Infertility affects a significant number of couples worldwide, with a prevalence of up to 15% among reproductive-aged individuals. Assisted reproductive technology (ART) has become a popular treatment option for infertility, and frozen-thawed embryo transfer (FET) is a widely used technique. Hormone replacement therapy (HRT) is used to prepare the endometrium for FET cycles, and estrogen supplementation is a crucial component of HRT. Oral and transdermal routes of estrogen administration have been utilized for endometrial preparation in FET cycles, but it is unclear which route of administration is more effective (Glujovsky et al., 2020).

There are differences between the oral and transdermal routes that may have implications for FET cycle outcomes. Oral estrogen is typically administered as an estradiol pill or tablet. After oral ingestion, the estrogen is absorbed in the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. The liver breaks down the estrogen into several metabolites, including estrone, which can stimulate the proliferation of endometrial cells. However, the liver also metabolizes estrogen into inactive metabolites, which can reduce the efficacy of the treatment. Additionally, oral estrogen can cause fluctuations in estrogen levels due to its rapid absorption and clearance from the body (Parish and Gillespie, 2017).

Transdermal estrogen, on the other hand, is typically administered as a patch or gel that is applied to the skin. The estrogen is absorbed through the skin and bypasses the first-pass metabolism in the liver, leading to more stable levels of estrogen in the body. Additionally, transdermal estrogen has been shown to have a lower risk of thromboembolic events compared to oral estrogen, which is an important consideration for patients with a history of thrombosis or other cardiovascular conditions (Mehta et al., 2021).

With the advancements in ART and vitrification technologies, FET has become increasingly popular (Roque et al., 2019; Shapiro et al., 2014). FET offers several advantages, including a reduced risk of ovarian hyperstimulation syndrome and ectopic pregnancy, the preservation of supernumerary embryos, and increased cumulative live birth rates (LBR) (Glujovsky et al., 2020; Rienzi et al., 2017). Studies have shown that FET can result in clinical pregnancy rates (CPR) comparable to or even higher than fresh embryo transfer. Endometrial preparation for FET can be achieved through natural, semi-natural, or HRT cycles (Banker et al., 2021; Mumusoglu et al., 2021).

Various endometrial preparation techniques have been proposed for FET in HRT cycles, with exogenous estrogen being supplied to promote endometrial development and prevent spontaneous ovulation (Abu-Musa et al., 1998; Devroey and Pados, 1998; Paulson, 2011; Ziegler and Russell, 1995). Estrogen can be administered through various routes, including oral tablets, transdermal patches or gel, or vaginal tablets (Krasnow et al., 1996; Li et al., 1992). A survey of 161 fertility doctors from 35 countries conducted in 2014 found that 86% of participants preferred the oral route, followed by the transdermal (8%), vaginal (3%), intramuscular (2%), and other routes (1%) (Weissman et al., 2014).

Synchronization of endometrial preparation with embryonic developmental stages is a crucial element to maximize endometrial receptivity and secure embryo implantation. HRT cycles offer a higher degree of flexibility in this regard without compromising LBR and are therefore more commonly preferred in clinical settings. Previous research has shown no difference in reproductive outcomes in patients undergoing HRT cycles, regardless of the route of estrogen administration (Ghobara et al., 2017; Zaat et al., 2021). However, no conclusive studies are available for comparing the clinical outcomes of various approaches to endometrial preparation. To compare the clinical outcomes of oral (tablets) versus transdermal (gel/patches) estrogen for endometrial preparation in GnRH agonist down-regulated HRT-frozen embryo transfer cycles, the present systematic review and meta-analysis was conducted.

METHODS

Protocol registration

The study was conducted following standard guidelines using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2015) and was registered with PROSPERO under the number **CRD42022342535**.

Ethics and dissemination

No ethical approval is required for this study, as it is a systematic review and meta-analysis of previously published studies. The results of this study will be disseminated through a peer-reviewed publication and conference presentations.

Eligibility criteria

Inclusion criteria

1. Randomized controlled trials (RCTs) comparing the use of oral and transdermal estrogen for endometrial preparation in HRT-FET cycles.
2. Studies published in English language.
3. Studies reporting on at least one of the following outcomes: CPR, LBR, endometrial thickness, cancellation rate, and adverse events.

Exclusion criteria:

1. Non-RCTs, observational studies, case reports, letters, and editorials.
2. Studies that compared oral and transdermal estrogen for non-endometrial preparation in HRT-FET cycles.
3. Studies that used other types of estrogen preparations (e.g., vaginal or injectable).

Search strategy

A comprehensive literature search was undertaken for all published articles up until May 30, 2022, in electronic databases including PubMed, Embase, Cochrane Library, Scopus, OVID Trip Database, and Google Scholar. The following key terms were used: "oral estrogen" OR "transdermal estrogen gel" OR "Oral" versus "Trans dermal E2 gel" OR "E2 versus oral" AND "FET" OR "frozen thawed embryo transfer" AND "Hormone Replacement Therapy" OR "HRT" AND "Endometrium preparation." Additionally, the reference list of retrieved studies and review articles was manually searched to retrieve relevant studies further, often missed while performing the electronic search.

Study selection

Two reviewers independently screened the titles and abstracts of the identified studies. The inclusion criteria were RCTs comparing oral and transdermal estrogen for endometrial preparation in HRT-FET cycles. Studies that did not report clinical outcomes or included patients with a history of uterine abnormalities, endometrial hyperplasia or cancer, or polycystic ovary syndrome (PCOS) were excluded. Any disagreement between the reviewers was resolved by discussion and consensus or by consulting a third reviewer.

Fig. 1. PRISMA flow diagram for the selection of studies and specific reasons for exclusion from the present meta-analysis.

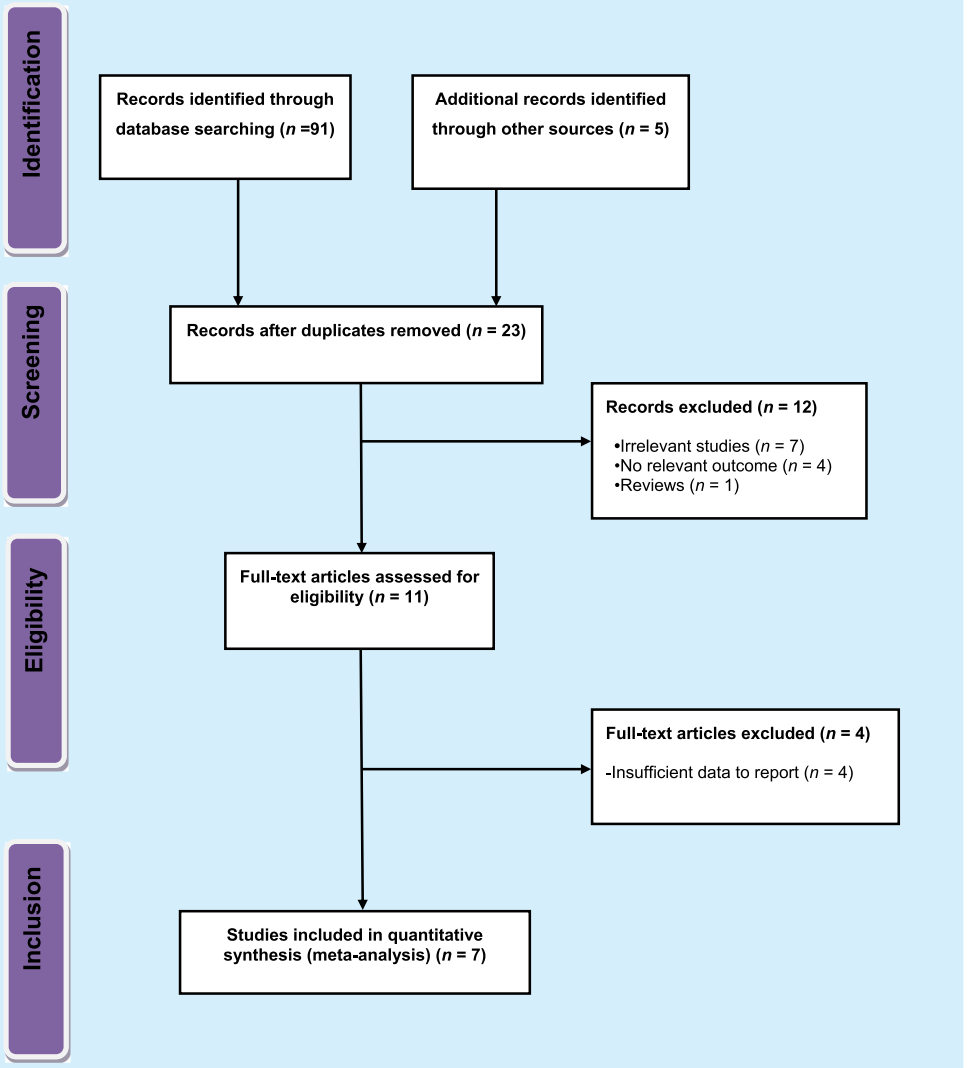


Table 1. Baseline characteristics of included studies in clinical outcomes of oral versus transdermal estrogen for endometrial preparation for frozen thawed embryo transfer in HRT-FET cycles.

S. No.	Author (year)	Country, study period	Study design	Investigated groups	Sample size	Age, years	BMI	Duration of infertility (years)	Duration of treatment (days)	Drugs used	Dosage	Outcome investigated
1.	Davar et al. (2016)	Iran April 2012–January 2013	RCT	Oral Transdermal patches	45 45	28.8 ± 4.3 28.8 ± 4.3	NA	6.3 ± 4.4 4.9 ± 3.4	NA	NA NA	6 mg of oral estradiol valerate 100 µg of 17-B estradiol transdermal patch	ET, CPR, MR, IR
2.	Ferrer-Molina et al. (2018)	Spain NA	RCT	Oral Transdermal patches	70 66	39.6 ± 4.8 39.6 ± 4.1	NA	3.9 ± 1.3 3.7 ± 2.6	NA	Meriestra Evopad	2 mg of oestradiol valerate Two 75-µg patches every second day from day 6 onward	ET, CPR, MR, IR, LBR
3.	Tehraninejad et al. (2018)	Iran September 2015–November 2016	RCT	Oral Transdermal patches	50 50	31.2 ± 6.5 33.0 ± 6.6	25.1 ± 4.2 25.8 ± 7.3	6.4 ± 5.2 6.2 ± 4.5	16.7 ± 4.1 17.5 ± 4.5	Progynova Oestrogel	8 mg/day of oestradiol valerate 17-beta estradiol 0.06%	MR, CPR, ET, LBR
4.	Kahraman et al. (2019)	Turkey May 2017–October 2017	RCT	Oral Transdermal patches	156 146	30.7 ± 3.9 31.5 ± 3.9	23.9 ± 3.4 23.9 ± 3.2	NA	NA	Estrofem Climara	2 mg three times per day estradiol tablets 3.9-mg of 17-beta estradiol 0.06%	ET, CPR, MR
5.	Kumari et al. (2021)	India November 2020–April 2021	RCT	Oral Transdermal gel	50 50	31.8 ± 3.8 32.6 ± 2.9	24.2 ± 3.1 24.8 ± 2.6	5.5 ± 2.2 6.0 ± 3.4	NA	Estradiol valerate 17β-estradiol gel	6 mg/day E2 1.25 g 0.06% gel	ET, CPR, PSS, MR, IR
6.	Patil et al. (2021)	India January 2018–December 2018	RCT	Oral Transdermal gel	66 20	31.8 ± 4.6 30.2 ± 4.3	25.9 ± 3.1 24.9 ± 3.7	NA	11.5 ± 4.7 15.7 ± 10.7	Estradiol valerate 17β-estradiol gel	NA	CPR, LBR
7.	Scheffer et al. (2021)	Brazil April 2018–February 2019	RCT	Oral Transdermal patches Transdermal gel	30 30 30	35.5 ± 3.8 35.6 ± 2.3 34.8 ± 3.4	24.2 ± 4.8 23.8 ± 2.1 24.2 ± 2.1	NA	NA	Primogyna Oestrogel Pump Estradot	NA	CPR

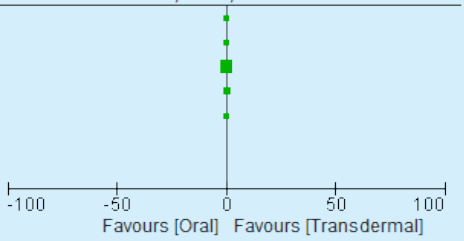
Notes: RCT, randomized controlled trial; ET, endometrial thickness; CPR, clinical pregnancy rate; LBR, live birth rate; MR, miscarriage rate; PSS, patient satisfaction score; CCR, cycle cancellation rate; IR, implantation rate.

Fig. 2 (A–E). Forest plot for (A) endometrial thickness; (B) implantation rate; (C) clinical pregnancy rate; (D) miscarriage rate; and (E) live birth rate in oral versus transdermal estrogen for frozen embryo transfer cycle.

(A)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Davar et al. 2016	8.7	1.2	45	8.4	0.9	45	12.3%	0.28 [-0.13, 0.70]
Jaya et al. 2021	9.4	0.8	50	9.4	0.8	50	13.8%	0.00 [-0.39, 0.39]
Kahraman et al. 2019	10.1	1.7	156	9.9	1.4	146	41.6%	0.13 [-0.10, 0.35]
Molina et al. 2018	7.6	1.6	70	7	1.8	66	18.5%	0.35 [0.01, 0.69]
Tehraninejad et al. 2018	8.6	1.2	50	8.5	1.4	50	13.8%	0.08 [-0.32, 0.47]
Total (95% CI)			**371**			**357**	**100.0%**	**0.16 [0.02, 0.31]**

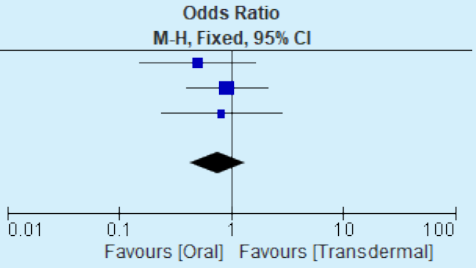
Heterogeneity: Chi² = 2.44, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)



(B)

Study or Subgroup	Oral Estrogen Events	Total	Transdermal Estrogen Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davar et al. 2016	5	45	9	45	31.8%	0.50 [0.15, 1.63]
Jaya et al. 2021	16	50	17	50	45.9%	0.91 [0.40, 2.10]
Scheffer et al. 2021	6	30	7	30	22.3%	0.82 [0.24, 2.81]
Total (95% CI)		**125**		**125**	**100.0%**	**0.76 [0.42, 1.38]**
Total events	27		33			

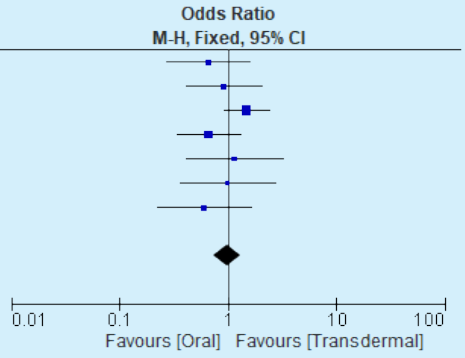
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)



(C)

Study or Subgroup	Oral Estrogen Events	Total	Transdermal Estrogen Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davar et al. 2016	12	45	16	45	12.1%	0.66 [0.27, 1.62]
Jaya et al. 2021	28	50	29	50	13.1%	0.92 [0.42, 2.03]
Kahraman et al. 2019	109	156	89	146	28.5%	1.49 [0.92, 2.39]
Molina et al. 2018	31	70	36	66	21.2%	0.66 [0.34, 1.30]
Patil et al. 2021	23	66	7	22	7.0%	1.15 [0.41, 3.21]
Scheffer et al. 2021	14	30	14	30	7.7%	1.00 [0.36, 2.76]
Tehraninejad et al. 2018	8	50	12	50	10.4%	0.60 [0.22, 1.63]
Total (95% CI)		**467**		**409**	**100.0%**	**0.98 [0.74, 1.31]**
Total events	225		203			

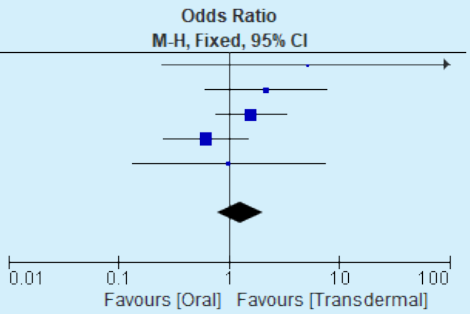
Heterogeneity: Chi² = 5.98, df = 6 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)



(D)

Study or Subgroup	Oral Estrogen Events	Total	Transdermal Estrogen Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Davar et al. 2016	2	45	0	45	1.6%	5.23 [0.24, 112.06]
Jaya et al. 2021	8	50	4	50	11.3%	2.19 [0.61, 7.81]
Kahraman et al. 2019	21	156	13	146	39.2%	1.59 [0.77, 3.31]
Molina et al. 2018	10	70	14	66	41.6%	0.62 [0.25, 1.51]
Scheffer et al. 2021	2	30	2	30	6.3%	1.00 [0.13, 7.60]
Total (95% CI)		**351**		**337**	**100.0%**	**1.28 [0.79, 2.06]**
Total events	43		33			

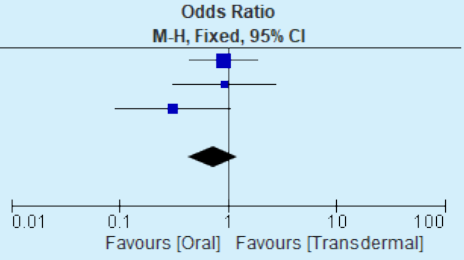
Heterogeneity: Chi² = 4.44, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.99 (P = 0.32)



(E)

Study or Subgroup	Oral Estrogen Events	Total	Transdermal Estrogen Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Molina et al. 2018	21	70	21	66	47.4%	0.92 [0.44, 1.90]
Patil et al. 2021	17	66	6	22	20.9%	0.93 [0.31, 2.75]
Tehraninejad et al. 2018	4	50	11	50	31.7%	0.31 [0.09, 1.05]
Total (95% CI)		**186**		**138**	**100.0%**	**0.73 [0.43, 1.23]**
Total events	42		38			

Heterogeneity: Chi² = 2.48, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.18 (P = 0.24)



Data extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form. The following data were extracted: study characteristics (author, year of publication, country, sample size, study design, and duration), patient characteristics (age, BMI, etc.), treatment characteristics (type of estrogen, dose, duration, and mode of administration), and clinical outcomes (CPR, implantation rate (IR), miscarriage rate (MR), ongoing pregnancy rate, LBR, endometrial thickness, and adverse events).

Quality assessment

The risk of bias (ROB) of the included studies was assessed independently by two reviewers using the Cochrane Collaboration's tool for assessing the ROB (Higgins et al., 2023). The following domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Any disagreement between the reviewers was resolved by discussion and consensus or by consulting a third reviewer.

Data synthesis and analysis

Statistical analysis was performed using Review Manager version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark). The pooled effect sizes were calculated as odds ratios (ORs) for categorical or standardized mean differences (SMDs) for continuous with 95% confidence intervals (CIs) using the fixed/random-effects model. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (Higgins and Thompson, 2002). Subgroup analysis was performed according to the type of estrogen and mode of administration.

Trial sequential analysis

Trial sequential analysis (TSA) was conducted with the guidelines of a former publication by Meng et al. (2018). To determine the necessary sample size, we chose a type I error significance of 5%. We then constructed the TSA monitoring boundaries using TSA software Version 0.9.5.10 Beta.

RESULTS

Literature selection

The initial search generated 96 records, as shown in Fig. 1, of which 23 records remained after the removal of duplicates. Following the exclusion of irrelevant studies and review articles, a total of 11 eligible articles were further evaluated for eligibility. Finally, after evaluating study details, four articles were removed due to insufficient data or overlapping data, leaving the current meta-analysis with a total of seven studies (Davar et al., 2016; Ferrer-Molina et al., 2018; Kahraman et al., 2019; Kumari et al., 2021; Patil et al., 2021; Scheffer et al., 2021; Tehraninejad et al., 2018).

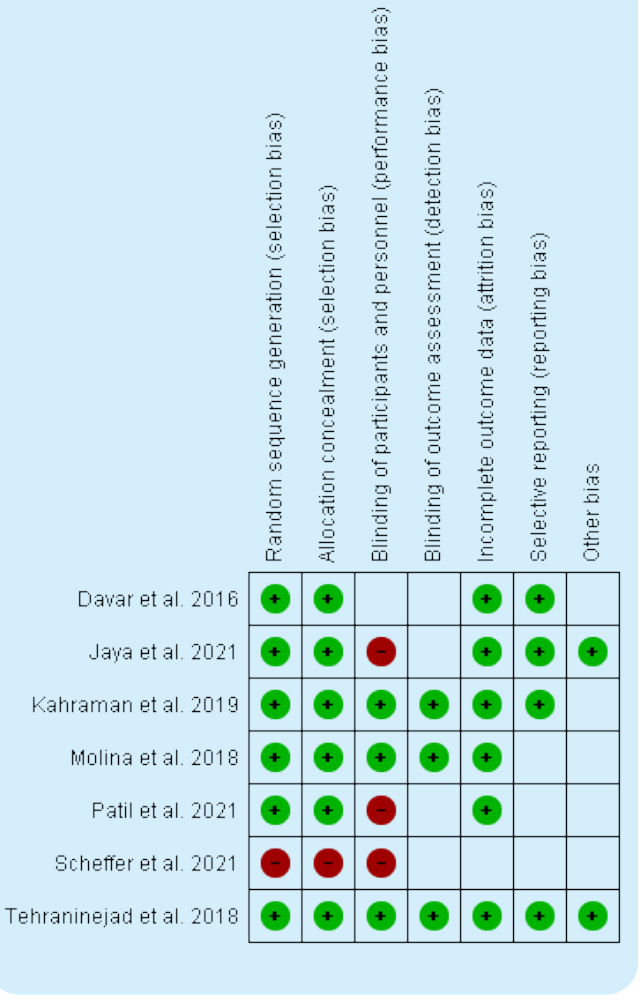
Study characteristics

Table 1 presents the details of the seven studies included in this meta-analysis, comprising a total of 898 patients undergoing in-vitro fertilization (IVF). The studies were published between 2016 and 2021, with sample sizes ranging from 30 to 156 IVF patients. Of the included studies, five were conducted in populations of Caucasian ethnicity, while two studies included populations of Asian ethnicity.

Endometrial thickness

The meta-analysis of five studies (Davar et al., 2016; Ferrer-Molina et al., 2018; Kahraman et al., 2019; Kumari et al., 2021; Tehraninejad et al., 2018) revealed significant variations in endometrial thickness

Fig. 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



(ET) between the oral and transdermal estrogen groups (SMD = 0.16; 95% CI = 0.02–0.31), as depicted in Fig. 2A. A fixed effects model was employed due to the considerable heterogeneity observed among the included studies (I^2 = 0%, p = 0.66).

Implantation rate

Out of the seven studies included, three (Davar et al., 2016; Kumari et al., 2021; Scheffer et al., 2021) provided data on IR. The meta-analysis showed no significant difference in IR between the oral and transdermal estrogen groups (OR = 0.76; 95% CI = 0.42–1.38), as presented in Fig. 2B. The included studies demonstrated no substantial heterogeneity (I^2 = 0%; p value = 0.71).

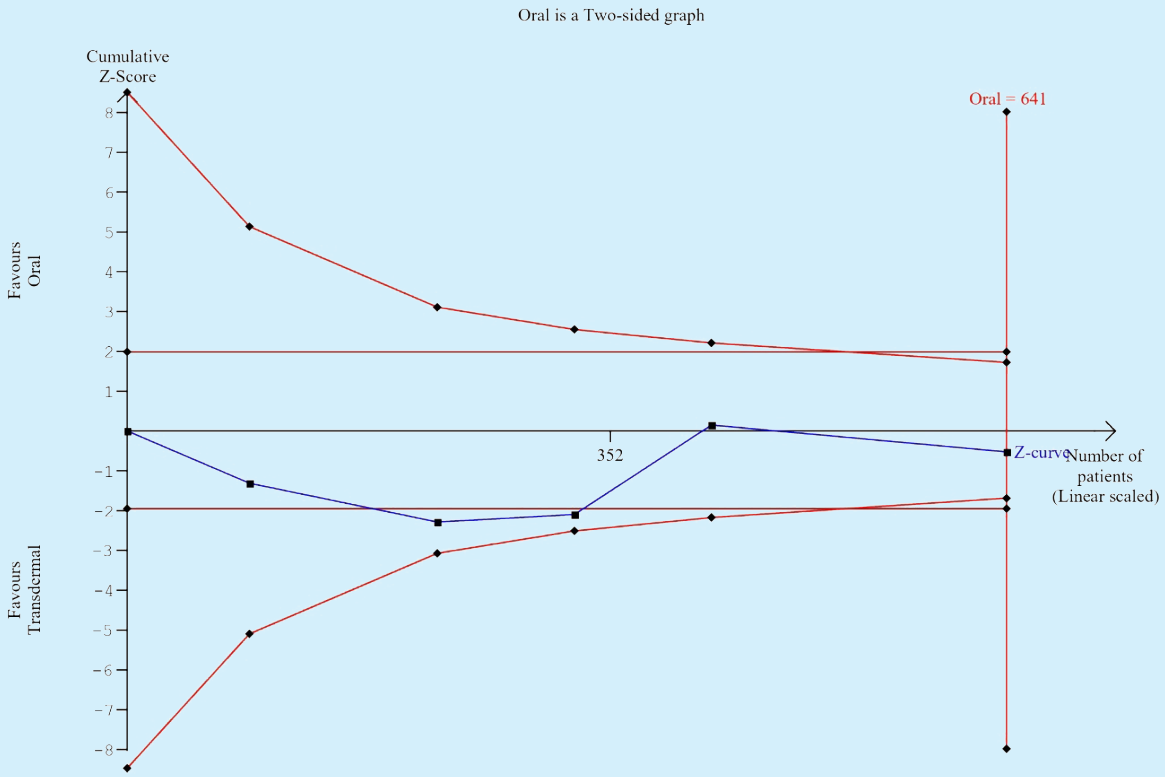
Clinical pregnancy rate

All seven studies (Davar et al., 2016; Ferrer-Molina et al., 2018; Kahraman et al., 2019; Kumari et al., 2021; Patil et al., 2021; Scheffer et al., 2021; Tehraninejad et al., 2018) provided data on clinical pregnancy rate (CPR). There was no significant difference in CPR between the oral and transdermal estrogen groups (OR = 0.98; 95% CI = 0.74–1.31), as illustrated in Fig. 2C. The included studies demonstrated no substantial heterogeneity (I^2 = 0%; p value = 0.43).

Miscarriage rate

A meta-analysis of five studies (Davar et al., 2016; Ferrer-Molina et al., 2018; Kahraman et al., 2019; Kumari et al., 2021; Scheffer et al., 2021) showed no significant association in miscarriage rate (MR)

Fig. 4. Trial sequential analysis for endometrial thickness in oral versus transdermal estrogen for frozen embryo transfer cycle.



between the oral and transdermal estrogen groups (OR = 1.28; 95% CI = 0.79–2.06), as depicted in Fig. 2D. However, there was a trend toward a higher MR in the transdermal estrogen group. The fixed-effects model was used due to the low heterogeneity observed among the included studies (I^2 = 0%; p value = 0.32).

Live birth rate

A meta-analysis of three studies (Ferrer-Molina et al., 2018; Patil et al., 2021; Tehraninejad et al., 2018) revealed no significant difference in live birth rate (LBR) between the oral and transdermal estrogen groups (OR = 0.73; 95% CI = 0.43 to 1.23), as presented in Fig. 2E. The included studies demonstrated no substantial heterogeneity (I^2 = 19%; p value = 0.29).

Quality assessment

Overall, most of the RCTs were assessed to have a low or unclear ROB (Fig. 3). The main sources of potential bias were unclear randomization and allocation concealment methods, as well as a lack of blinding for participants and personnel.

Trial sequential analysis

The TSA results are presented in Fig. 4. The required sample size was determined to be 641 samples, and the cumulative z-curve crossed the trial sequential monitoring boundary before reaching the required sample size. This indicates that the conclusions drawn from the analysis are robust, with sufficient evidence to support them.

DISCUSSION

The meta-analysis included a total of seven studies, involving 898 IVF patients. Overall, most of the RCTs were assessed to have a low or unclear ROB. The main sources of potential bias were unclear randomization and allocation concealment methods, as well as a lack of blinding for participants and personnel. The meta-analysis showed that the endometrial thickness was significantly higher in the transdermal estrogen group than in the oral estrogen group. These results suggest that transdermal estrogen may be more effective in promoting endometrial growth for FET in HRT-FET cycles than oral estrogen.

The use of exogenous estrogen for endometrial preparation is a crucial step in FET cycles. In recent years, there has been a growing interest in comparing the clinical outcomes of different routes of estrogen administration, specifically oral versus transdermal administration. The current systematic review and meta-analysis aimed to evaluate the differences in clinical outcomes between these two routes of administration in HRT-FET cycles. In an updated Cochrane Review, Ghobara et al. (2017) assessed various endometrial preparation methods, including clomiphene and gonadotropins, in comparison to HRT-FET cycles with or without GnRH agonist down-regulation. The endometrial preparation techniques varied and included true or modified natural cycles, as well as other FET regimens. However, there was insufficient evidence to recommend one regimen over another in women with regular ovulatory cycles undergoing frozen-thawed embryo transfer.

The lack of significant differences in LBR, CPR, and MR between the two groups is also consistent with previous studies (Patil et al., 2021; Scheffer et al., 2021). However, it is important to note that the included studies had varying patient populations, sample sizes, and study designs, which may have contributed to the heterogeneity observed in the meta-analysis. The results of this meta-analysis have important implications for clinical practice. While there may be no significant differences in clinical outcomes between oral and transdermal estrogen administration, the finding that transdermal administration may result in a thicker endometrial lining may be of particular interest to clinicians. In cases where endometrial thickness is a concern, transdermal administration may be a preferred route of administration.

We acknowledge that future studies should consider including other types of cycles to further explore the clinical outcomes of oral versus transdermal estrogen for endometrial preparation in different cycle types.

Chen et al. (2016) reported a significantly higher (two times) risk of preeclampsia in HRT-FET cycles compared with that in fresh transfer cycles in women who were diagnosed with polycystic ovary syndrome. The possible reason is that the supra-physiologic number of corpora lutea in fresh transfer cycles could produce the circulating vasoactive factors and protect pregnancies against hypertensive disorders of pregnancy (HDP) compared with natural cycles (NC). Additionally, enterohepatic circulation plays a crucial role in maintaining the stability of estrogen levels, particularly when estrogen is administered orally (Hu et al., 2023). It is important to note that pregnancy outcomes other than live births are important in light of the increased risk of pre-eclampsia associated with HRT-FET cycles (Racca et al., 2023).

It is worth noting that this meta-analysis has several limitations. First, the included studies had varying patient populations, which may limit the generalizability of the results. Second, the included studies had different protocols for estrogen administration, which may have contributed to the heterogeneity observed in the meta-analysis. Finally, the included studies did not report on the long-term effects of estrogen administration, such as the risk of venous thromboembolism.

CONCLUSION

The current meta-analysis suggests that there may be no significant differences in clinical outcomes between oral and transdermal estrogen administration for endometrial preparation in HRT-FET cycles. However, transdermal administration may result in a thicker endometrial lining, which may be of interest to clinicians. Further studies are needed to better understand the long-term effects of estrogen administration and to determine the optimal preparation.

ACKNOWLEDGMENTS

None.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication. Please contact the authors for the details.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

FUNDING

No funding was received.

ORCID

Peter Humaidan https://orcid.org/0000-0001-6884-5366
Kshitiz Murdia https://orcid.org/0000-0002-0682-6327
Vipin Chandra https://orcid.org/0000-0003-2288-2481
Nihar Bhoi https://orcid.org/0000-0002-2238-2033
Isha Suwalka https://orcid.org/0000-0001-8340-5967
Ritu Punhani https://orcid.org/0000-0001-6107-911X

REFERENCES

Abu-Musa A, Hannoun A, Khalil A, Masaad Z, Karam K. Artificial endometrial preparation for oocyte donation using synthetic estrogen and progestogen. Clin Exp Obstet Gynecol. 1998; 25:83–5.

Banker M, Arora P, Banker J, Shah S. A comparative study to assess the efficacy of two different estradiol formulations during in Vitro fertilization. Int J Reprod Med. 2021;2021:3153307.

Chen Z-J, Shi Y, Sun Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016;375: 523–33.

Davar R, Janati S, Mohseni F, Khabazkhoob M, Asgari S. A comparison of the effects of transdermal estradiol and estradiol valerate on endometrial receptivity in frozen-thawed embryo transfer cycles: a randomized clinical trial. J Reprod Infertil. 2016;17:97–103.

Devroey P, Pados G. Preparation of endometrium for egg donation. Hum Reprod Update. 1998;4:856–61.

Ferrer-Molina P, Calatayud-Lliso C, Carreras-Collado R, et al. Oral versus transdermal oestrogen delivery for endometrial preparation before embryo transfer: a prospective, comparative, randomized clinical trial. Reprod Biomed Online. 2018;37:693–702.

Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst Rev. 2017;7:CD003414.

Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar AM, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev. 2020;10: CD006359.

Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial [Internet]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. Cochrane; 2023 [cited 2023 Feb 21]. Available from: https://training.cochrane.org/handbook/current/chapter-08

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.

Hu S, Ding Q, Zhang W, Kang M, Ma J, Zhao L. Gut microbial beta-glucuronidase: a vital regulator in female estrogen metabolism. Gut Microbes [Internet]. 2023 [cited 2024 Mar 13];15:2236749. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10416750/

Kahraman S, Çetinkaya CP, Sahin Y, Oner G. Transdermal versus oral estrogen: clinical outcomes in patients undergoing frozen-thawed single blastocyst transfer cycles without GnRHa suppression, a prospective randomized clinical trial. J Assist Reprod Genet. 2019;36:453–9.

Krasnow JS, Lessey BA, Naus G, Hall LL, Guzick DS, Berga SL. Comparison of transdermal versus oral estradiol on endometrial receptivity. Fertil Steril. 1996;65:332–6.

Kumari J, Nayar KD, Gupta S, Sanan S, Mehra P. A prospective randomized comparative study between transdermal estradiol gel and oral estradiol valerate tablets for successful clinical outcome in frozen-thawed embryo transfer cycles. Fertil Sci Res [Internet]. 2021 [cited 2022 Jul 15];8:83–91. Available from: https://www.fertilityscienceresearch.org/article.asp?issn=2394-4285;year=2021;volume=8;issue=1;spage=83;epage=91;aulast=Kumari

Li TC, Cooke ID, Warren MA, Goolamallee M, Graham RA, Aplin JD. Endometrial responses in artificial cycles: a prospective study comparing four different oestrogen dosages. Br J Obstet Gynaecol. 1992;99:751–6.

Mehta J, Kling JM, Manson JE. Risks, benefits, and treatment modalities of menopausal hormone therapy: current concepts. Front Endocrinol [Internet]. 2021 [cited 2023 Feb 22];12:564781. Available from: https://pubmed.ncbi.nlm.nih.gov/33841322/

Meng J, Wang S, Zhang M, Fan S, Zhang L, Liang C. TP73 G4C14-A4T14 polymorphism and cancer susceptibility: evidence from 36 case-control studies. Biosci Rep. 2018;38:BSR20181452.

Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

Mumusoglu S, Polat M, Ozbek IY, et al. Preparation of the endometrium for frozen embryo transfer: a systematic review. Front Endocrinol [Internet]. 2021 [cited 2022 Jul 24];12:688237. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8299049/

Parish SJ, Gillespie JA. The evolving role of oral hormonal therapies and review of conjugated estrogens/bazedoxifene for the management of menopausal symptoms. Postgrad Med. 2017;129:340–51.

Patil M, Venkatappa KG, Patil M. Comparison of art outcome in frozen embryo transfer cycle using oral estradiol valerate and estradiol transdermal gel. Onco Fertil J [Internet]. 2021 [cited 2022 Oct 11];4:14. Available from: https://www.tofjonline.org/article.asp?issn=2589-9597;year=2021;volume=4;issue=1;spage=14;epage=26;aulast=Patil;type=0

Paulson RJ. Hormonal induction of endometrial receptivity. Fertil Steril. 2011;96:530–5.

Racca A, Santos-Ribeiro S, Drakopoulos P, et al. Clinical pregnancy rate for frozen embryo transfer with HRT: a randomized controlled pilot study comparing 1 week versus 2 weeks of oestradiol priming. Reprod Biol Endocrinol RBE [Internet]. 2023 [cited 2024 Mar 13];21:62. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10326948/

Rienzi L, Gracia C, Maggiulli R, et al. Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance. Hum Reprod Update. 2017;23:139–55.

Roque M, Haahr T, Geber S, Esteves SC, Humaidan P. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. Hum Reprod Update. 2019;25:2–14.

Scheffer JB, Scheffer BB, de Aguiar APS, Franca JB, Lozano DM, Fanchin R. A comparison of the effects of three different estrogen used for endometrium preparation on the outcome of day 5 frozen embryo transfer cycle. JBRA Assist Reprod. 2021;25:104–8.

Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. Fertil Steril. 2014;102:3–9.

Tehraninejad ES, Kabodmehri R, Hosein Rashidi B, et al. Trans dermal estrogen (oestrogel) for endometrial preparation in freeze embryo transfer cycle: an RCT. Int J Reprod Biomed [Internet]. 2018 [cited 2022 Jul 9];16:51–6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5899770/

Weissman A, Leong M, Sauer MV, Shoham Z. Characterizing the practice of oocyte donation: a web-based international survey. Reprod Biomed Online. 2014;28:443–50.

Zaat T, Zagers M, Mol F, Goddijn M, van Wely M, Mastenbroek S. Fresh versus frozen embryo transfers in assisted reproduction. Cochrane Database Syst Rev. 2021;2:CD011184.

Ziegler WF, Russell JB. High success with gestational carriers and oocyte donors using synchronized cycles. J Assist Reprod Genet. 1995;12:297–300.