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Impact of endometrial thickness on reproductive outcome in fresh and frozen–thawed embryo transfer: systematic review and meta-analysis

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KEYWORDS: assisted reproduction; clinical pregnancy; ectopic pregnancy; embryo implantation; embryo transfer; endometrial thickness; infertility; live birth; miscarriage

ABSTRACT

Objective *To evaluate the impact of endometrial thickness on the reproductive outcomes of embryo transfer (ET) treatments using both cut-off-based meta-analysis and meta-analysis of proportions.*

Methods *This was a systematic review and meta-analysis of comparative studies (randomized controlled trials, cohort studies, case–control studies) and descriptive studies (cross-sectional studies, case series) published in English, French, German, Italian or Spanish and analyzing the impact of endometrial thickness on the rates of embryo implantation, clinical pregnancy, live birth, miscarriage and/or ectopic pregnancy in fresh and/or frozen–thawed ET cycles. Live-birth rate was defined as the primary outcome. The literature search was conducted in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Web of Science and ÍnDICEs-CSIC, from inception of each database until 1 September 2024. The risk of bias was assessed using the Newcastle–Ottawa scale for analytical studies and the Joanna Briggs Institute tool for descriptive studies. Pooled effects were estimated as odds ratios (OR) or risk differences obtained from a random-effects model, with 95% CIs. Linear meta-regression was used to assess the relationship between risk difference and endometrial thickness cut-off. Meta-analysis of proportions was performed as a secondary analysis, comparing outcome rates between 2-mm intervals of endometrial thickness and a reference category (≥ 6 to < 8 mm).*

Results *A total of 67 studies were included, of which 22 were cohort studies and 45 were descriptive. In fresh ET cycles, the live-birth rate was higher in patients with a thicker endometrium across cut-offs from ≥ 5 mm (OR, 5.66 (95% CI, 1.10–28.98)) to ≥ 15 mm (OR, 1.49 (95% CI, 1.26–1.77)). Effect size decreased linearly as the cut-off increased* ($P < 0.0001$; $R^2 = 61.5\%$). *Meta-analysis of proportions found significant differences in live-birth rate when the reference category (≥ 6 to < 8 mm) (0.26 (95% CI, 0.22–0.30);* $I^2 = 94.3\%$) *was compared to the groups with endometrial thickness of ≥ 4 to < 6 mm (0.17 (95% CI, 0.14–0.20);* $I^2 = 0\%$), *≥ 10 to*

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< 12 mm (0.35 (95% CI, 0.28–0.42); $I^2 = 99.2\%$), ≥ 12 to < 14 mm (0.43 (95% CI, 0.33–0.53); $I^2 = 99.5\%$) and ≥ 14 to < 16 mm (0.39 (95% CI, 0.27–0.51); $I^2 = 99.2\%$). In frozen–thawed ET cycles, thicker endometrium was associated with a higher live-birth rate for cut-offs between ≥ 5 mm (OR, 2.65 (95% CI, 1.23–5.72); $I^2 = 0\%$) and ≥ 8 mm (OR, 1.17 (95% CI, 1.10–1.24); $I^2 = 13\%$). A linear relationship between endometrial thickness and effect size was observed for this analysis ($P < 0.0001$; $R^2 = 73.8\%$). In fresh ET cycles, endometrial thickness was correlated positively with the rates of clinical pregnancy and embryo implantation, inversely with miscarriage rate and showed no correlation with ectopic pregnancy. In frozen–thawed ET cycles, thicker endometrium was correlated positively with the rate of clinical pregnancy and inversely with that of miscarriage. Evidence quality was rated as very low in 70% of assessments because of bias and inconsistency.

Conclusions *Endometrial thickness is associated with reproductive outcomes, but demonstrates a gradient of effectiveness as a prognostic indicator, rather than offering a critical threshold below which ET should be avoided. ET scheduling should consider endometrial thickness alongside other prognostic factors. © 2025 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

During the follicular phase of the ovarian cycle, the endometrial thickness increases as a result of the proliferation of its functional layer, both in the natural cycle and in assisted reproductive treatments involving the transfer of fresh or frozen–thawed embryos. Endometrial growth represents one of the estrogen-induced morphological and functional changes involved in the preparation of the endometrium for embryo implantation. In a clinical setting, endometrial thickness can be measured repeatedly and reproducibly using high-resolution transvaginal ultrasound[1,2], which has generated interest over several decades in evaluating its use as a marker of endometrial receptivity[3,4]. Indeed, ultrasonographic measurement of endometrial thickness during the advanced proliferative phase is considered a prognostic factor for endometrial receptivity to embryo implantation[5–9]. The majority of original research studies and meta-analyses published to date support the association between endometrial thickness and the effectiveness of embryo transfer (ET) treatments. However, despite this association, a definitive threshold for endometrial thickness associated with critical rates of embryo implantation, clinical pregnancy, live birth, miscarriage and ectopic pregnancy is yet to be identified. A minimal endometrial thickness of 7–8 mm is frequently accepted in clinical practice, although this threshold has limited ability to discriminate between favorable and unfavorable outcomes in ET cycles[7,10].

The aim of the present study was to analyze the impact of endometrial thickness on the reproductive outcomes of ET treatments using an updated quantitative synthesis, focusing on relevant outcomes overlooked in previous meta-analyses, such as ectopic pregnancy. Our primary cut-off-based analysis was complemented by two additional approaches: first, linear regression analysis of the relationship between effect size and endometrial thickness cut-off value, and second, estimation of outcome probabilities across different intervals of endometrial thickness. The second approach aims to avoid the cumulative estimation effect associated with threshold-based analysis.

METHODS

This systematic review and meta-analysis was registered prospectively in the PROSPERO database (registration number: CRD42024569911).

Eligibility criteria

The population of interest was infertile women undergoing fresh or frozen–thawed ET, for whom endometrial preparation was by artificial cycle (sequential administration of exogenous estrogens and progesterone), and for whom endometrial thickness was measured using transvaginal ultrasound, either on the day of triggering (with human chorionic gonadotropin or other agents) in the case of fresh ET, or on the day of initiating exogenous progesterone in the case of frozen–thawed ET.

We defined the following inclusion criteria. (1) Comparative study (randomized controlled trial, cohort study or case–control study) or descriptive study (cross-sectional study or case series) that analyzed or described the effect of endometrial thickness on the rates of embryo implantation, clinical pregnancy, live birth, miscarriage and/or ectopic pregnancy. (2) Measurement of endometrial thickness was performed using high-resolution transvaginal ultrasound, as part of ET cycle monitoring. (3) Results were expressed in the appropriate terms to be summarized into the quantitative synthesis. (4) Peer-reviewed article that was published in English, French, German, Italian or Spanish from inception of the database until 1 September 2024.

The exclusion criteria were defined as follows. (1) Study assessed the effect of endometrial thickness on the outcome of intrauterine insemination. (2) Endometrial thickness was measured on a date other than the day of triggering, in the case of fresh ET, or that of initiating exogenous progesterone, in the case of frozen–thawed ET. (3) Insufficient information provided on the population, exposure, outcomes or comparisons of interest. (4) Dataset not compliant with the requirements of data extraction for the meta-analysis.

Information sources and search strategy

We performed a systematic literature search in the following databases: MEDLINE, EMBASE, Cochrane

Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, Web of Science (including Web of Science Core Collection, Current Contents Connect, Derwent Innovations Index, Grants Index, KCI–Korean Journal Database, ProQuest Citation Index and SciELO Citation Index) and ÍnDICEs-CSIC. The search strategy was structured using the specific syntax of each database (Appendix S1). We searched for articles published in the abovementioned languages with no time restrictions. The first search was conducted on 1 July 2024, and the search was rerun on 1 September 2024. Cross-references cited in reviewed studies were identified manually.

Selection of studies and data extraction

Studies identified by the literature search were classified initially according to their title and abstract by pairs of authors, each author working independently. Studies deemed eligible by both authors were evaluated in full-text format, and discrepancies were resolved by consensus with a third author (either F.P.-M. or M.C.-C.).

The independent variable was endometrial thickness, defined as the linear distance between two external endometrial boundaries, measured in the region of maximum endometrial thickness. Measurement was by transvaginal ultrasound scan on the day of triggering in the case of fresh ET, or on the day of initiating exogenous progesterone in the case of frozen–thawed ET.

The exposure was defined as endometrial thickness greater than or equal to the cut-off value, which was used to dichotomize the distribution of transfer cycles according to endometrial thickness. Non-exposed patients were those with endometrial thickness below the cut-off value.

The primary outcome was the live-birth rate, defined according to the International Glossary on Infertility and Fertility Care[11]. Secondary outcomes were the rates of embryo implantation, clinical pregnancy, miscarriage and ectopic pregnancy, defined as per the aforementioned consensus.

Data were extracted from the selected studies by one of a pair of authors and verified by the second author. Collected data included year of publication, study design, study period, study setting, study population (type of ET, inclusion and exclusion criteria), procedure for measurement of endometrial thickness, use of endometrial features as a criterion for cancellation of ET, cut-off values and/or intervals of endometrial thickness analyzed, number of exposed and non-exposed patients, outcomes considered and control of potential confounders (age, body mass index, smoking status, type and cause of infertility, number and quality of embryos transferred and day of ET). Disagreements between authors on the results of data extraction were resolved by a third review of the original study, conducted jointly by the two evaluators.

Risk-of-bias assessment for individual studies

Non-randomized comparative studies were evaluated using the Newcastle–Ottawa scale (NOS) for cohort studies[12]. The following domains were analyzed: selection of participants, comparability of exposed and non-exposed cohorts, and assessment of the outcome. Results were summarized by a numerical score and qualified according to the standards of the United States Agency for Healthcare Research and Quality (AHRQ)[13]. Cross-sectional studies and case series were assessed using the Joanna Briggs Institute (JBI) critical appraisal tool (jbi.global/critical-appraisal-tools).

Quality assessment was carried out by pairs of authors, each author working independently. Disagreements were resolved by a third review of the original study, conducted jointly by the two evaluators. All selected studies were included in the quantitative synthesis, irrespective of their quality, although a sensitivity analysis for study quality was conducted.

Effect measures and synthesis methods

Numerical data were transcribed as reported by the original authors, and missing data were noted. When results were reported in terms of intervals of endometrial thickness, standardization was performed by defining 1-mm intervals including values greater than or equal to a given integer thickness and less than the next consecutive integer thickness (i.e. from $\geq n$ mm to $< n+1$ mm). When reproductive outcomes were reported in terms of strata of endometrial thickness (defined by a threshold), cumulative frequencies above or below specific cut-off points were calculated by summing the frequencies of the relevant strata. Data were recorded in a predesigned Excel spreadsheet (Microsoft, Redmond, WA, USA).

Quantitative synthesis of the selected studies was performed if at least two studies with sufficient consistency for the pooled analysis were available. The primary analysis concerned the estimation of the effect of endometrial thickness on reproductive outcome, stratified by as many cut-off values as were reported by the selected studies, by means of odds ratios (OR) and risk differences, with 95% CIs. To obtain these estimates, a fixed-effects or random-effects meta-analysis model was applied, depending on the clinical and statistical heterogeneity of the studies. The association between the estimated risk difference and the endometrial thickness cut-off value, which was assumed to be a potential source of heterogeneity, was analyzed by linear meta-regression. The secondary analysis comprised a meta-analysis of proportions based on the results of all the studies that provided adequate data. The effects were analyzed by estimating the pooled proportion of each outcome for each 2-mm interval of endometrial thickness and by pairwise comparison of each interval with a reference category (≥ 6 to < 8 mm). The association between the estimated proportion and endometrial thickness was evaluated by linear meta-regression.

The primary and secondary analyses were carried out separately for fresh and frozen–thawed ET. Statistical heterogeneity of the pooled analyses was estimated using Cochran's Q test and the I^2 statistic. The Q statistic was considered statistically significant if $P < 0.05$. I^2

was graded according to the criteria of Higgins and Thompson[14]; values above 50% were considered to represent high heterogeneity.

The following sensitivity analyses were conducted: (1) including only cohort studies scoring ≥ 7 on the NOS assessment and rated as good quality according to AHRQ criteria, to consider the effect of study design and quality; (2) excluding studies that analyzed artificial ET cycles but included a minority subset of natural or modified–natural cycles without reporting the results separately and (3) excluding studies that considered endometrial thickness or pattern as a criterion for ET cancellation. The relevance of the sensitivity analyses was interpreted by considering the variation of the summary effect measures compared with the overall analysis, as well as heterogeneity estimators.

Risk-of-bias assessment across studies

Reporting bias and small-size study effects were evaluated by visual assessment of the asymmetry of funnel plots for each outcome. Egger's test was used where necessary.

Certainty assessment

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria were applied to rate the quality of the evidence supporting the estimates for each outcome[15]. The baseline confidence rating was adjusted after considering the risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose–response gradient and potential effects of confounding factors. The confidence ratings of the pooled results are presented for each outcome and each comparison.

RESULTS

A total of 579 distinct references were identified during the initial search of databases and registers and subsequent cross-reference searches, of which 225 were evaluated for their eligibility in full-text format and 69 were included in the quantitative synthesis[16–84] (Figure 1). The study characteristics are described in Appendix S2. Twenty-three were cohort studies, of which three were prospective[16–18] and 20 were retrospective[19–37,83]. The remaining 45 were descriptive studies[38–82,84]. Appendix S2 also summarizes

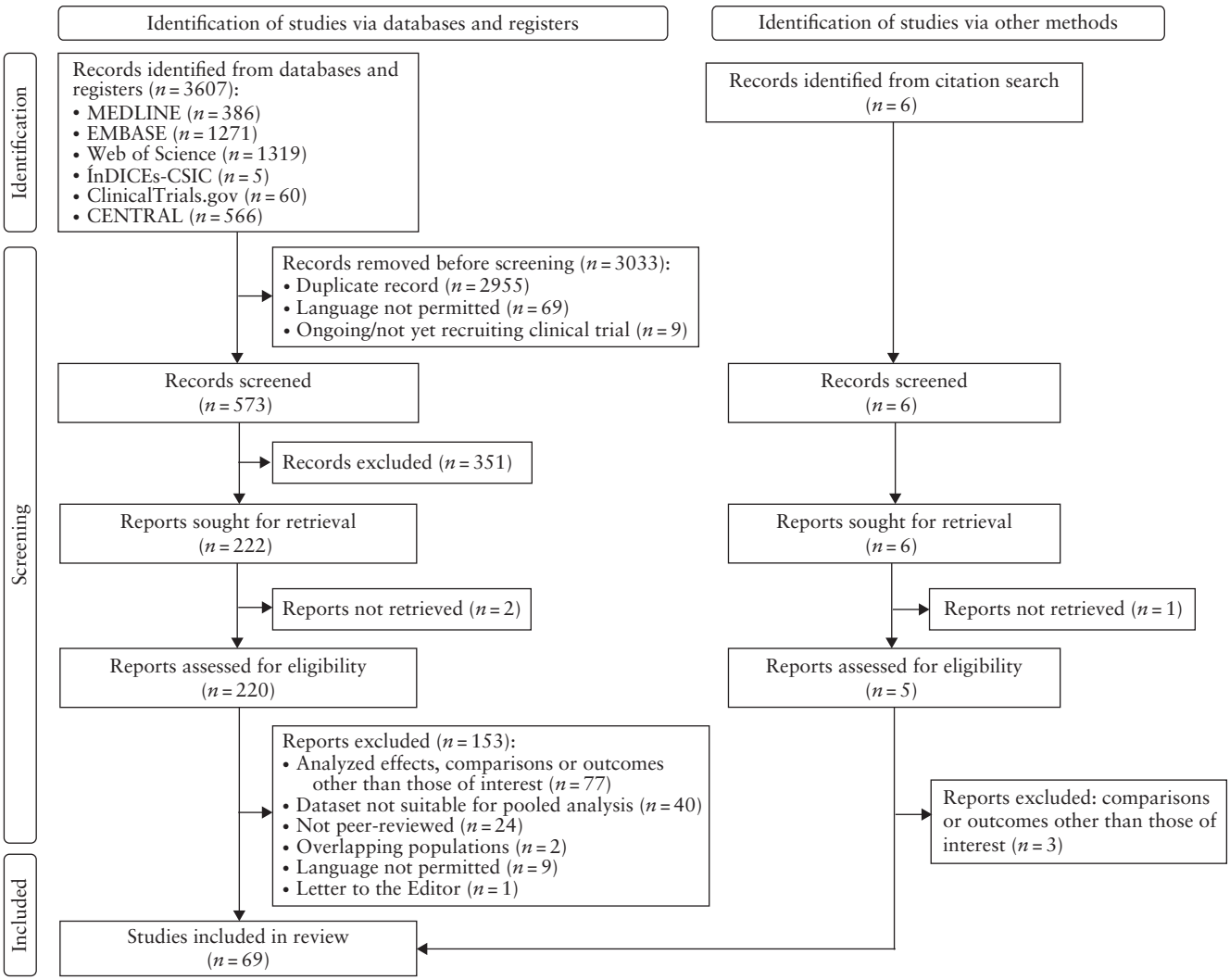

Figure 1 Flowchart summarizing study selection process. CENTRAL, Cochrane Central Register of Controlled Trials.

the excluded studies and the reason for exclusion, as well as the assessment of quality and risk of bias in the included studies. Of the included studies, approximately 10% were rated as low quality (2/22 cohort studies and 5/45 descriptive studies), mainly because of the lack of comparability between the exposed and unexposed groups in the case of cohort studies and the lack of control for potentially relevant confounders in the case of descriptive studies. The results of individual included studies are presented in forest plots in Appendix S3.

Quantitative synthesis

Fresh embryo transfer cycles

Live birth. The analysis included 22 studies that were scored predominantly as being of good or fair quality[18,21,26–29,32,34–37,42,50,60–62,65,67,70,73,75,79]. Table 1 provides a summary of the estimated effects of endometrial thickness cut-offs between 4 and 18 mm. Estimates based on a random-effects model, identified a significant association between a thicker endometrial lining and an increased live-birth rate following fresh ET for all cut-off values between ≥ 5 mm (OR, 5.66 (95% CI, 1.10–28.98)) and ≥ 15 mm (OR, 1.49 (95% CI, 1.26–1.77)), with a significant linear decrease in effect size as the cut-off increased ($y = -0.0151x + 0.257$; $P < 0.0001$; $R^2 = 61.5\%$) (Appendix S4). Figure 2a shows the meta-regression of effect size (expressed as risk differences) by endometrial thickness cut-off.

In the sensitivity analysis including only cohort studies with a NOS score ≥ 7 and rated as good quality according to AHRQ standards, the size of the estimated effects did not change significantly (Appendix S5). Exclusion of studies in which ET was cancelled based on endometrial thickness or pattern did not reveal relevant changes in global estimates (Appendix S5).

Meta-analysis of proportions revealed significant differences in the estimated live-birth rate when the reference group (≥ 6 to < 8 mm) (0.26 (95% CI, 0.22–0.30); $I^2 = 94.3\%$) was compared to the groups with endometrial thickness of ≥ 4 to < 6 mm (0.17 (95% CI, 0.14–0.20); $I^2 = 0\%$), ≥ 10 to < 12 mm (0.35 (95% CI, 0.28–0.42); $I^2 = 99.2\%$), ≥ 12 to < 14 mm (0.43 (95% CI, 0.33–0.53); $I^2 = 99.5\%$) and ≥ 14 to < 16 mm (0.39 (95% CI, 0.27–0.51); $I^2 = 99.2\%$) (Appendix S6). Linear meta-regression detected a significant positive correlation between live-birth rate and endometrial thickness.

Clinical pregnancy. The quantitative synthesis for clinical pregnancy included 51 studies[16–22,25,26,28,29,33–43,45–52,54–58,60,61,63–66,68–71,74,75,79,81,83,84] analyzing the effect of endometrial thickness dichotomized by cut-offs between 4 and 23 mm. The studies were pooled using a random-effects model. Women with a thicker endometrium had a significantly higher rate of clinical pregnancy following fresh ET for cut-off values ranging from ≥ 5 mm (OR, 11.02 (95% CI, 2.23–54.46); $I^2 = 13\%$) to ≥ 17 mm (OR, 1.44 (95% CI, 1.01–2.06); $I^2 = 0\%$) (Appendix S4). Within this range of cut-off

Table 1 Effect of endometrial thickness (stratified by cut-offs) on live-birth rate following fresh or frozen–thawed embryo transfer (ET)

Endometrial thickness cut-off	*Fresh ET*					*Frozen–thawed ET*				
	Studies (n)	*Live births per ET**		*OR (95% CI)*	I^2 (%)	*Studies* (n)	*Live births per ET**		*OR (95% CI)*	I^2 (%)
		≥ *Cut-off*	< *Cut-off*				≥ *Cut-off*	< *Cut-off*		
4 mm	1	7133/21888 (32.6)	0/26 (0)	25.62 (1.56–420.50)	—	1	5325/18919 (28.1)	0/23 (0)	18.41 (1.12–303.17)	—
5 mm	4	11 203/33997 (33.0)	9/118 (7.6)	5.66 (1.10–28.98)	55†	2	5413/19172 (28.2)	7/57 (12.3)	2.65 (1.23–5.72)	0
6 mm	10	45 134/130052 (34.7)	226/1516 (14.9)	2.36 (1.79–3.12)	57†	6	22 233/74265 (29.9)	100/577 (17.3)	1.89 (1.22–2.92)	55
7 mm	16	54 482/149830 (36.4)	1229/5765 (21.3)	1.90 (1.61–2.23)	75†	5	21 595/72107 (29.9)	456/2091 (21.8)	1.52 (1.27–1.81)	35
8 mm	13	43 719/119647 (36.5)	4012/15561 (25.8)	1.61 (1.34–1.93)	91†	8	20 609/68887 (29.9)	3381/12252 (27.6)	1.17 (1.10–1.24)	13
9 mm	11	19 970/49072 (40.7)	3881/15137 (25.6)	1.51 (1.44–1.58)	0	5	721/2294 (31.4)	1111/3628 (30.6)	0.93 (0.68–1.27)	77†
10 mm	10	33 955/84956 (40.0)	16 852/54584 (30.9)	1.47 (1.24–1.75)	97†	5	6532/21007 (31.1)	10 654/34893 (30.5)	1.06 (1.03–1.11)	0
11 mm	9	16 078/38313 (42.0)	11 890/32570 (36.5)	1.35 (1.07–1.72)	96†	3	105/211 (49.8)	855/1668 (51.3)	1.13 (0.84–1.53)	0
12 mm	8	11 256/26649 (42.2)	24 328/74906 (32.5)	1.32 (1.13–1.53)	87†	4	2191/7122 (30.8)	14 539/48134 (30.2)	1.05 (1.00–1.11)	0
13 mm	7	7433/13775 (54.0)	20 457/51431 (39.8)	1.44 (1.21–1.72)	88†	2	23/49 (46.9)	916/1750 (52.3)	0.87 (0.43–1.76)	19
14 mm	6	4173/9373 (44.5)	30 629/88019 (34.8)	1.28 (1.04–1.57)	81†	4	661/2177 (30.4)	16 984/55996 (30.3)	1.02 (0.93–1.13)	0
15 mm	8	3278/6617 (49.5)	28 933/71538 (40.4)	1.49 (1.26–1.77)	78†	1	0/2 (0)	95/285 (32.3)	0.40 (0.02–8.39)	—
16 mm	2	158/499 (31.7)	15 699/53151 (29.5)	1.10 (0.91–1.33)	0	2	155/490 (31.6)	15 710/53174 (29.5)	1.11 (0.91–1.34)	0
17 mm	3	86/475 (18.1)	8204/21259 (38.6)	0.56 (0.14–2.15)	92†	1	0/0 (0)	95/287 (33.1)	NE	—
18 mm	1	42/136 (30.9)	15 728/53241 (29.5)	1.07 (0.74–1.53)	—	1	42/136 (30.9)	15 728/53241 (29.5)	1.07 (0.74–1.53)	—

*Data are given as *n*/*N* (%), unless stated otherwise. †Cochran's Q test *P*-value < 0.05. NE, not estimable; OR, odds ratio.

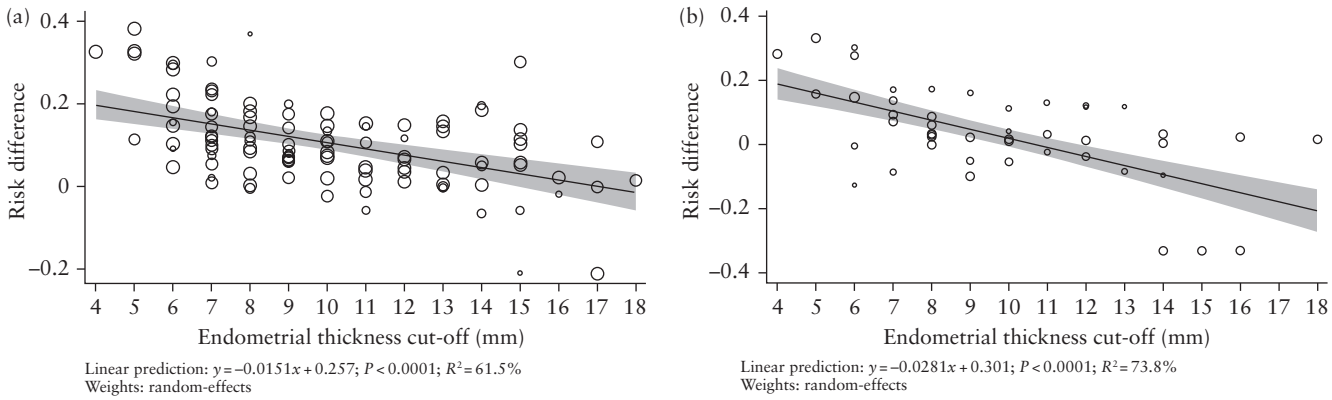

Figure 2 Estimated effect of endometrial thickness (stratified by cut-offs) on live-birth rate: linear meta-regression based on a random-effects model for fresh (a) and frozen–thawed (b) embryo transfer. Line indicates linear prediction and shading represents 95% CI. Individual studies are denoted by circles, where the diameter is proportional to the weight of the study in the meta-analysis estimate.

values, the effect size was associated linearly and inversely with the cut-off used to categorize endometrial thickness ($y = -0.0195x + 0.323$; $P < 0.0001$; $R^2 = 71\%$) (Appendix S4). Sensitivity analyses including only good-quality cohort studies and excluding studies that considered endometrial thickness or pattern as a criterion for ET cancellation did not show any relevant changes in estimated effects (Appendix S5). Meta-analysis of proportions estimated a clinical pregnancy rate of 0.32 (95% CI, 0.26–0.37; $I^2 = 97.7\%$) for fresh ET cycles with endometrial thickness of ≥ 6 to < 8 mm (Appendix S6). This was significantly lower compared with estimates for ≥ 10 to < 12 mm (0.44 (95% CI, 0.38–0.50); $I^2 = 98.4\%$), ≥ 12 to < 14 mm (0.49 (95% CI, 0.42–0.56); $I^2 = 98.2\%$) and ≥ 16 to < 18 mm (0.47 (95% CI, 0.38–0.56); $I^2 = 48.8\%$). Nevertheless, meta-regression did not reveal a significant linear correlation (Appendix S6).

Embryo implantation. Six descriptive studies[50,56,57,60,65,68], all of which were rated as high quality using the JBI tool, reported on embryo implantation. Random-effects meta-analysis found a significant association between increased endometrial thickness and a higher implantation rate following fresh ET for all cut-off values between 6 and 16 mm, with the exception of 12 mm and 15 mm (Appendix S4). The size of this effect decreased progressively from ≥ 6 mm (OR, 3.72 (95% CI, 2.04–6.76); $I^2 = 0\%$) to ≥ 14 mm (OR, 1.21 (95% CI, 1.10–1.33); $I^2 = 0\%$). The meta-regression identified a significant linear correlation between the endometrial thickness cut-off and the implantation rate ($y = -0.0171x + 0.300$; $P < 0.0001$; $R^2 = 28.6\%$) (Appendix S4). Sensitivity analysis for cohort study quality was not feasible, because all of the studies included in this meta-analysis were descriptive. The sensitivity analysis excluding studies in which ET was canceled because of endometrial thickness or pattern did not show substantial changes in the overall estimates (Appendix S5).

The meta-analysis of proportions was based on two studies[50,57], and each of the estimates was based on data from a single study. The estimated rate of embryo implantation following fresh ET for the reference category was 0.17 (95% CI, 0.13–0.21). All pairwise comparisons with the other categories revealed significant differences (Appendix S6). There was a linear significant increase in the rate of embryo implantation as endometrial thickness increased ($y = 0.032x - 0.004$; $P < 0.0001$; $R^2 = 82.0\%$).

Miscarriage. The random-effects meta-analysis, based on the results of 22 observational studies[18,21,25–29,34,36–38,45,50,52,60–62,65,68,70,73,75], demonstrated that increased endometrial thickness was associated significantly with lower miscarriage rate following fresh ET for cut-off values between ≥ 6 mm (OR, 0.57 (95% CI, 0.39–0.81); $I^2 = 0\%$) and ≥ 10 mm (OR, 0.63 (95% CI, 0.41–0.98); $I^2 = 96\%$) (Appendix S4). Above ≥ 10 mm, significant differences were detected upon stratifying by some cut-off values (≥ 12, ≥ 14 and ≥ 15 mm) but not by others (≥ 11, ≥ 13, ≥ 16 and ≥ 17 mm). The meta-regression between the size effect and the endometrial thickness cut-off revealed a significant linear correlation ($y = 0.0138x - 0.205$; $P < 0.05$; $R^2 = 19.1\%$) (Appendix S4). Sensitivity analyses that included only good-quality cohort studies and excluded studies that cancelled ET cycles based on endometrial thickness or pattern yielded similar results (Appendix S5). Although meta-regression detected a linear correlation, meta-analysis of proportions revealed no significant differences in miscarriage rate between the reference category of endometrial thickness and thinner or thicker ranges (Appendix S6).

Ectopic pregnancy. The random-effects meta-analysis of seven studies[26,29,34,37,38,61,82] identified significant differences in the rate of ectopic pregnancy for four cut-off values (≥ 8, ≥ 10, ≥ 12 and 15 mm) (Appendix S4). The linear meta-regression was not significant ($y = -0.0001x - 0.130$; $P > 0.05$; $R^2 = 0$) (Appendix S4). In the sensitivity analysis including only good-quality cohort studies, only the estimated difference at the 15-mm cut-off remained significant (Appendix S5). The sensitivity analysis excluding studies in which the

endometrial thickness or pattern was applied as a criterion for ET cancellation estimated a significant reduction in the rate of ectopic pregnancy at several cut-offs, without a recognizable linear pattern (Appendix S5). Meta-analysis of proportions, based on two studies[37,82], did not detect significant differences in estimates between the reference category and other categories of endometrial thickness (Appendix S6).

Frozen–thawed embryo transfer cycles

Live birth. The random-effects meta-analysis, which included nine studies[18,23,28,30,35,37,59,73,78], found an association between increased live-birth rate in frozen–thawed ET cycles and greater endometrial thickness for cut-offs between ≥ 5 mm (OR, 2.65 (95% CI, 1.23–5.72); $I^2 = 0\%$) and ≥ 8 mm (OR, 1.17 (95% CI, 1.10–1.24); $I^2 = 13\%$), and additionally for ≥ 10 mm (OR, 1.06 (95% CI, 1.03–1.11); $I^2 = 0\%$) (Table 1). The changes in effect size per cut-off point, expressed by risk difference, were linearly adjusted ($y = -0.0281x + 0.301$; $P < 0.0001$; $R^2 = 73.8\%$) (Figure 2b, Appendix S4). A sensitivity analysis including only good-quality cohort studies revealed significant differences for only the ≥ 6, ≥ 7, ≥ 8 and ≥ 10 mm cut-offs (Appendix S5). After excluding data from three studies that analyzed a limited number of endometrial preparations other than standard artificial cycles[30,37,59], the estimates of effect size and direction did not change significantly (Appendix S5). Finally, the sensitivity analysis considering only studies that did not cancel ET cycles based on endometrial thickness or pattern identified significant differences in the live-birth rate for five cut-offs (≥ 5, ≥ 6, ≥ 7, ≥ 8 and ≥ 10 mm) (Appendix S5). Meta-analysis of proportions did not reveal significant differences when the reference category of endometrial thickness was compared with thicker or thinner categories (Appendix S6). The value of the coefficient of determination (R^2) for the meta-regression was 0%.

Clinical pregnancy. The meta-analysis on clinical pregnancy rate included 12 studies that analyzed the effect of endometrial thickness in the range of 4–18 mm[18,23,24,28,30,35,37,53,59,72,76,78]. Estimates indicated that frozen-thawed ET cycles performed with endometrial thickness above the cut-off, in the range of 6–8 mm, had a significantly higher rate of clinical pregnancy, but that the magnitude of this effect decreased progressively as the cut-off value increased (≥ 6 mm: OR, 1.82 (95% CI, 1.41–2.36), $I^2 = 23\%$; ≥ 8 mm: OR, 1.19 (95% CI, 1.10–1.28), $I^2 = 36\%$) (Appendix S4). Significant differences in the clinical pregnancy rate were also determined at ≥ 10, ≥ 12 and ≥ 14 mm cut-offs. The effects of endometrial thickness on the clinical pregnancy risk difference were linearly adjusted ($y = -0.0148x + 0.217$; $P < 0.05$; $R^2 = 69.2\%$) (Appendix S4). Sensitivity analysis including only good-quality cohort studies estimated significant differences in the frequency of clinical pregnancy at lower cut-off points (≥ 6, ≥ 7, ≥ 8, ≥ 10 and ≥ 12 mm) (Appendix S5). The sensitivity analysis excluding studies that considered some natural or modified–natural cycles[30,37,59,76] provided similar results (Appendix S5). The sensitivity analysis excluding studies that cancelled ET based on endometrial thickness or pattern showed that a thicker endometrium was favored at several cut-offs (≥ 6, ≥ 7, ≥ 8, ≥ 9, ≥ 10 and ≥ 12 mm) (Appendix S5). The clinical pregnancy rate following frozen–thawed ET for each considered 2-mm interval of endometrial thickness, estimated by meta-analysis of proportions, did not differ significantly from that of the reference category (Appendix S6).

Embryo implantation. Estimates for embryo implantation could not be determined because of a lack of data that could be aggregated for a pooled analysis for more than one cut-off value (Appendix S4). Sensitivity analysis was not feasible for the same reason (Appendix S5).

Miscarriage. A random-effects meta-analysis based on data from seven studies[18,28,30,37,59,73,80] revealed a significant difference in the risk of miscarriage following frozen–thawed ET only for the ≥ 6 mm cut-off (OR, 0.54 (95% CI, 0.29–0.99); $I^2 = 0\%$) (Appendix S4). This was also true for the sensitivity analysis excluding studies that cancelled ET based on a thin endometrium or unfavorable endometrial pattern (Appendix S5). However, meta-regression analysis identified a significant linear correlation between endometrial thickness cut-off and miscarriage rate ($y = 0.051x - 0.485$; $P < 0.0005$), albeit with a 0% coefficient of determination (Appendix S4). The estimated miscarriage rate in the meta-analysis of proportions did differ significantly between the reference category and any other category (Appendix S6).

Ectopic pregnancy. Data on the effects of endometrial thickness on ectopic pregnancy rate were derived from five studies[31,37,59,77,80]. Aggregate estimates, based on a random-effects model, showed a decreased rate of ectopic pregnancy following frozen–thawed ET in cycles with endometrial thickness at or above the threshold for four of the five cut-off values analyzed (≥ 8, ≥ 10, ≥ 12 and ≥ 14 mm) (Appendix S4). The linear meta-regression did not indicate a statistically significant correlation between endometrial thickness cut-off and the magnitude of impact on the rate of ectopic pregnancy ($y = -0.0005x - 0.014$; $P > 0.05$; $R^2 = 4.5\%$) (Appendix S4). The quality-based sensitivity analysis included data from only two good-quality cohort studies[31,37], and found a significantly higher rate of ectopic pregnancy in cycles performed in women with a thinner endometrium for the 8-mm cut-off (Appendix S5). All overall estimates were derived from studies that included some non-artificial cycles, so their exclusion for the purpose of sensitivity analysis rendered it impossible to obtain estimates for any cut-off values (Appendix S5). Sensitivity analysis excluding studies in which ET was canceled because of endometrial thickness or pattern did not show any relevant changes compared

with the overall analysis (Appendix S5). The meta-analysis of proportions was based on two studies[37,77] and did not detect significant differences between the reference category and any other category (Appendix S6).

Risk of bias across studies

Funnel plots in Appendix S7 illustrate reporting bias and the potential impact of small-study effects for each comparison included in the main analysis. This evaluation was complemented by Egger's test (Appendix S7). It was determined that reporting bias might affect some of the cut-off-based analysis of fresh ET cycles for live birth and clinical pregnancy, and that of frozen ET cycles for miscarriage.

Certainty of evidence

Appendix S8 summarizes the quality of evidence and certainty of the estimated effects according to GRADE criteria. Certainty of evidence was rated as very low in 70% of assessments, both for the primary outcome and the analysis as a whole.

DISCUSSION

Several previous meta-analyses have evaluated the relationship between endometrial thickness and the outcome of ET[5–9,85]: six focused on fresh ET cycles, analyzing endometrial thickness cut-offs at the time of triggering[5–9,85], and two of these also analyzed the effect of endometrial thickness measured on the day of exogenous progesterone initiation in frozen–thawed ET cycles[7,85]. The studies of Momeni *et al.*[5] and Wu *et al.*[9] compared mean endometrial thickness between cycles with and those without subsequent pregnancy. Furthermore, Kasius *et al.*[6] and Craciunas *et al.*[7] assessed the discriminative ability of endometrial thickness using the area under the receiver-operating-characteristics curve, sensitivity, specificity, predictive values and likelihood ratios.

Regarding fresh ET cycles, our study analyzed live birth as the primary outcome, whereas previous meta-analyses by Kasius *et al.*[6] and Gao *et al.*[85] combined live birth with ongoing pregnancy as a composite outcome. Liao *et al.*[8] analyzed separately the live-birth rate using two strata (<7 mm *vs* >7 mm and >14 mm *vs* 7–14 mm). Our study found a significant linear association between greater endometrial thickness and increased live-birth rate across a wide range of cut-off values (5–15 mm), which is consistent with the findings of Gao *et al.*[85] and Liao *et al.*[8], but contrasts with those of Kasius *et al.*[6], albeit with limited comparability between the studies. In our study, the meta-analysis of proportions aligns with the cut-off-based analysis, which reinforces the reliability of our findings because the meta-analysis of proportions is not affected by the cumulative effect that could bias the cut-off-based approach. According to our estimates of risk difference, the harmful effect of performing ET with an endometrial thickness <7 mm decreases by half when it is performed with an endometrial thickness <12 mm.

Clinical pregnancy is the outcome that has been analyzed most widely by previous studies, which have reported consistently a detrimental effect of a thinner endometrium, in terms of both mean comparisons[5,9] and cut-off-based analysis[6–8,85]. The studies of Kasius *et al.*[6] and Craciunas *et al.*[7] reported lower rates of clinical pregnancy for a thinner endometrium, with a gradual decline in effectiveness as cut-off values increased[6,7], a pattern also reflected in our analysis. In the present study, meta-analysis of proportions revealed a lower clinical pregnancy rate in the reference category compared with categories of greater endometrial thickness. Estimations of risk difference suggested a relevant decrease in clinical pregnancy rate when fresh ET cycles with endometrial thickness <7 mm were compared with those with <12 mm. Implantation rates followed a similar trend.

The miscarriage rate was associated inversely with endometrial thickness, as reported in the literature[8,85]. Our study, which expanded the range of cut-off values compared with previous analyses, found significant differences between exposed and non-exposed cycles at several cut-offs in a discontinuous pattern. However, meta-analysis of proportions did not identify significant differences between the reference category and any other category, possibly because of the small number of included studies. No significant effects on ectopic pregnancy were identified by meta-analysis of proportions, although even fewer primary studies were available for this outcome.

Regarding frozen–thawed ET cycles, we found an association between live-birth rate and endometrial thickness in line with the findings of Gao *et al.*[85], although these authors analyzed the composite variable of live birth plus ongoing pregnancy. A similar concordance was observed in the analysis of clinical pregnancy[85]. For both outcomes, our analysis indicated a significantly lower respective rate in ET cycles with a thinner endometrium across multiple cut-off values. However, these associations were not continuous, and meta-analysis of proportions did not detect significant differences between the reference category of endometrial thickness and any other category. A significant association between endometrial thickness and miscarriage rate was found only for the ≥ 6-mm cut-off, although the 95% CI nearly includes 1. Although meta-regression of the cut-off-based analysis showed a significant linear trend of decreasing miscarriage risk with increasing endometrial thickness threshold, this was not supported by the meta-analysis of proportions. For ectopic pregnancy, the risk was lower with a thicker endometrium at cut-offs of ≥ 8, ≥ 10, ≥ 12 and ≥ 14 mm, but neither the linear trend nor the meta-analysis of proportions was significant.

We acknowledge several limitations to our meta-analysis, notably the non-randomized nature of most studies, the predominance of descriptive over analytical study designs and the preponderance of retrospective over prospective study types. According to Mathyk *et al.*[10], clinical heterogeneity affecting included studies

derives from differences in sample size, cut-off values, study design, control of confounders and potential selection bias. Our study controlled for some sources of heterogeneity, such as the type of treatment (fresh ET *vs* frozen–thawed ET) and the day of measurement of endometrial thickness, which was an inclusion criterion. Furthermore, no studies reported on the accuracy of ultrasound measurement, which is a potential source of bias.

The quantitative synthesis included mainly studies rated as being of good or fair quality; sensitivity analyses focused on the quality rating did not reveal substantial changes in results. Some estimates, especially those related to extreme categories of endometrial thickness, were derived from a small number of studies, limiting the generalizability and accuracy of the analyses. In addition, seven studies included natural or modified–natural ET cycles without reporting the results separately. This limitation was addressed by a specific sensitivity analysis when feasible. The evidence supporting these findings was rated as very low in certainty, due mainly to risk of bias and imprecision.

Other limitations of our study include language restrictions and changes in clinical procedures over time. Sensitivity analyses regarding study quality, type of frozen–thawed ET cycle and cancellation of ET cycles based on endometrial thickness or pattern did not reveal relevant changes in the estimates, although these potential confounding effects cannot be excluded completely. Adjustments were made to ensure consistency across studies and to make it possible to perform the pooled analysis, and substantial statistical heterogeneity required the use of random-effects models. The coefficient of determination of some meta-regressions was low, which may limit the accuracy or even the reliability of some inferences. The heterogeneity of the interval limits and cut-off values of the primary studies precluded the inclusion of some studies in the meta-analysis of proportions, which had to be constructed for 2-mm intervals of endometrial thickness to obtain more accurate estimates. The reference category of ≥ 6 to < 8 mm was chosen because it includes 7 mm, the most commonly accepted prognostic cut-off for ET, assuming a variability of around ± 1 mm in the transvaginal ultrasound measurement of endometrial thickness[2]. We deliberately did not evaluate the discriminative ability of ET, as no critical cut-offs were identified in the literature for clinical decision-making. Obstetric and perinatal outcomes were also excluded from this analysis.

Our results support the association of endometrial thickness on the day of triggering in fresh ET cycles with the rates of live birth, clinical pregnancy, embryo implantation and miscarriage. For frozen–thawed ET cycles, endometrial thickness on the first day of exogenous progesterone supplementation showed a positive linear correlation with the rates of live birth and clinical pregnancy and a negative correlation with miscarriage rate. Furthermore, an inverse association between endometrial thickness and the rate of ectopic pregnancy was identified in frozen–thawed ET cycles, although correlation analysis was not in accordance. Nevertheless, the rating of certainty supporting these findings was mostly low, and moderate in a few analyses. Therefore, recommendations should be stated as 'weak in favor' of considering endometrial thickness as a prognostic factor for these outcomes, according to the GRADE system. The risk difference estimates provide a practical approach for decision-making in ET scheduling, suggesting that a threshold of 12 mm (or 9 mm for frozen–thawed cycles) reduces the adverse impact of 'thin endometrium' on reproductive outcomes by half. These findings align with the meta-analyses of proportions.

In conclusion, our results do not support a minimum critical endometrial thickness below which ET should be avoided, but rather suggest a gradient of effectiveness. Given the low or very low certainty of the evidence supporting these findings, further well-designed and adequately powered randomized controlled trials are warranted to better assess the effects of endometrial thickness intervals on the outcome of ET.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Search strategy and results

Appendix S2 Selection and quality assessment of studies

Appendix S3 Results of individual studies

Appendix S4 Main analysis of secondary outcomes

Appendix S5 Sensitivity analyses

Appendix S6 Meta-analysis of proportions

Appendix S7 Assessment of reporting bias

Appendix S8 GRADE assessment of certainty of evidence

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Impacto del grosor endometrial en el resultado reproductivo en la implantación de embriones frescos y congelados-descongelados: revisión sistemática y metaanálisis

RESUMEN

Objetivo. Evaluar el impacto del grosor endometrial en los resultados reproductivos de los tratamientos de implantación de embriones (IE) utilizando tanto metaanálisis basado en puntos de corte como metaanálisis de proporciones.

Métodos. Este estudio fue una revisión sistemática y metaanálisis de estudios comparativos (ensayos controlados aleatorizados, estudios de cohortes, estudios de casos y controles) y estudios descriptivos (estudios transversales, series de casos) publicados en inglés, francés, alemán, italiano o español y que analizan el impacto del grosor endometrial en las tasas de implantación embrionaria, embarazo clínico, nacimientos vivos, aborto y/o embarazo ectópico en ciclos de IE frescos y/o congelados-descongelados. La tasa de nacimientos vivos se definió como el resultado primario. La búsqueda bibliográfica se realizó en MEDLINE, EMBASE, Registro Central Cochrane de Ensayos Controlados, ClinicalTrials.gov, Web of Science e 'InDICEs-CSIC, desde el inicio de cada base de datos hasta el 1 de septiembre de 2024. El riesgo de sesgo se evaluó mediante la escala de Newcastle-Ottawa para los estudios analíticos y la herramienta del Instituto Joanna Briggs para los estudios descriptivos. Los efectos combinados se estimaron como razón de momios (RM) o diferencias de riesgo obtenidas a partir de un modelo de efectos aleatorios, con IC del 95%. Se utilizó la metarregresión lineal para evaluar la relación entre la diferencia de riesgo y el punto de corte del grosor endometrial. Se realizó un metaanálisis de proporciones como análisis secundario, en el que se compararon las tasas de resultados entre intervalos de 2 mm del grosor endometrial y una categoría de referencia (≥6 a <8 mm).

Resultados. Se incluyó un total de 67 estudios, de los cuales 22 eran estudios de cohortes y 45 descriptivos. En los ciclos de IE en fresco, la tasa de nacimientos vivos fue mayor en las pacientes con un endometrio más grueso en los intervalos de ≥5 mm (RM 5,66 [IC 95%, 1,10–28,98]) a ≥15 mm (RM 1,49 [IC 95%, 1,26–1,77]). El tamaño del efecto disminuyó linealmente a medida que aumentaba el punto de corte (P<0,0001; R2 =61,5%). El metaanálisis de proporciones halló diferencias significativas en la tasa de nacimientos vivos cuando se comparó la categoría de referencia (≥6 a <8 mm) (0,26 (IC 95%, 0,22–0,30); I2 =94,3%) con los grupos con grosor endometrial de ≥4 a <6mm (0.17 (IC 95%, 0,14–0,20); I2 =0%), de ≥10 a <12mm (0,35 (IC 95%, 0,28–0,42); I2 =99,2%), de ≥12 a <14mm (0,43 (IC 95%, 0,33–0,53); I2 =99,5%) y de ≥14 a <16mm (0,39 (IC 95%, 0,27–0,51); I2 =99,2%). En los ciclos de IE congelados-descongelados, un endometrio más grueso se asoció con una mayor tasa de nacimientos vivos para puntos de corte entre ≥5mm (RM 2,65 [IC 95%, 1,23–5,72]; I2 =0%) y ≥8mm (RM 1,17 [IC 95%, 1,10–1,24]; I2 =13%). En este análisis se observó una relación lineal entre el grosor endometrial y el tamaño del efecto (P<0,0001; R2 =73,8%). En los ciclos de IE en fresco, el grosor endometrial se correlacionó positivamente con las tasas de embarazo confirmado ecográficamente e implantación embrionaria, inversamente con la tasa de abortos y no mostró correlación con el embarazo ectópico. En los ciclos de IE congelados-descongelados, el endometrio más grueso se correlacionó positivamente con la tasa de embarazo confirmado ecográfica e inversamente con la de aborto. La calidad de las pruebas se calificó como muy baja en el 70% de las evaluaciones debido a los sesgos y las inconsistencias.

Conclusiones. El grosor del endometrio está asociado con los resultados reproductivos, pero demuestra un gradiente de eficacia como indicador pronóstico, en lugar de ofrecer un umbral crítico por debajo del cual debe evitarse la IE. La programación de la IE debe tener en cuenta el grosor endometrial junto con otros factores pronósticos.

子宫内膜厚度对新鲜及冻融胚胎移植周期生殖结局的影响：系统综述与荟萃分析

摘要

目的 采用界值法荟萃分析与比例荟萃分析双重方法，评估子宫内膜厚度对胚胎移植（ET）治疗生殖结局的影响。

方法 本系统综述与荟萃分析纳入以英语、法语、德语、意大利语或西班牙语发表的比较性研究（随机对照试验、队列研究、病例对照研究）及描述性研究（横断面研究、病例系列），这些研究分析了新鲜和/或冻融ET周期中子宫内膜厚度对胚胎着床率、临床妊娠率、活产率、流产率和/或异位妊娠率的影响。活产率被定义为主要结局指标。文献检索覆盖MEDLINE、EMBASE、Cochrane对照试验中央注册库、ClinicalTrials.gov、Web of Science及InDICEs-CSIC数据库，检索时间自各数据库建库至2024年9月1日。采用纽卡斯尔-渥太华量表评估分析性研究的偏倚风险，使用乔安娜·布里格斯研究所工具评估描述性研究的偏倚风险。

通过随机效应模型估算合并效应值，以比值比（OR）或风险差及其95%置信区间（CI）表示。采用线性荟萃回归分析风险差与子宫内膜厚度界值的关系。作为次要分析，实施比例荟萃分析，比较以2毫米为间隔的子宫内膜厚度分组与参照组（≥6至<8毫米）的结局率差异。

结果 共纳入67项研究，其中22项为队列研究，45项为描述性研究。在新鲜ET周期中，子宫内膜厚度较厚者的活产率在所有界值（从≥5毫米（OR=5.66，95% CI：1.10-28.98））至≥15毫米（OR=1.49，（95% CI：1.26-1.77））均更高，且效应量随界值升高呈线性下降（P<0.0001；R^2=61.5%）。

参照组（≥6至<8毫米）的活产率为0.26（95% CI：0.22-0.30；I^2=94.3%），比例荟萃分析显示，与子宫内膜厚度≥4至<6毫米组（0.17，95% CI：0.14-0.20；I^2=0%）、≥10至<12毫米组（0.35，95% CI：0.28-0.42；I^2=99.2%）、≥12至<14毫米组（0.43，95% CI：0.33-0.53；I^2=99.5%）及≥14至<16毫米组（0.39，95% CI：0.27-0.51；I^2=99.2%）之间存在显著差异。在冻融ET周期中，较厚子宫内膜与较高活产率相关，界值范围从≥5毫米（OR=2.65，95% CI：1.23-5.72；I^2=0%）至≥8毫米（OR=1.17，95% CI：1.10-1.24；I^2=13%），且子宫内膜厚度与效应量存在线性关系（P<0.0001；R^2=73.8%）。在新鲜ET周期中，子宫内膜厚度与临床妊娠率和胚胎着床率呈正相关，与流产率负相关，与异位妊娠率无相关性。在冻融ET周期中，较厚子宫内膜与临床妊娠率正相关，与流产率负相关。因存在偏倚和不一致性，70%的评估证据质量被评定为极低。

结论 子宫内膜厚度与生殖结局相关，但其作为预后指标呈现出效果梯度变化，而非提供一个应避免实施ET的临界阈值（即低于此值则应避免进行胚胎移植）。

ET周期安排应结合其他预后因素综合考量子宫内膜厚度。