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Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis

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BACKGROUND: Early reproductive failure is the most common complication of pregnancy with only 30% of conceptions reaching live birth. Establishing a successful pregnancy depends upon implantation, a complex process involving interactions between the endometrium and the blastocyst. It is estimated that embryos account for one-third of implantation failures, while suboptimal endometrial receptivity and altered embryo–endometrial dialogue are responsible for the remaining two-thirds. Endometrial receptivity has been the focus of extensive research for over 80 years, leading to an indepth understanding of the processes associated with embryo–endometrial cross-talk and implantation. However, little progress has been achieved to translate this understanding into clinically meaningful prognostic tests and treatments for suboptimal endometrial receptivity.

OBJECTIVE AND RATIONALE: The objective of this systematic review was to examine the evidence from observational studies supporting the use of endometrial receptivity markers as prognostic factors for pregnancy outcome in women wishing to conceive, in order to aid clinicians in choosing the most useful marker in clinical practice and for informing further research.

SEARCH METHODS: The review protocol was registered with PROSPERO (CRD42017077891). MEDLINE and Embase were searched for observational studies published from inception until 26 February 2018. We included studies that measured potential markers of endometrial receptivity prior to pregnancy attempts and reported the subsequent pregnancy outcomes. We performed association and accuracy analyses using clinical pregnancy as an outcome to reflect the presence of receptive endometrium. The Newcastle–Ottawa scale for observational studies was employed to assess the quality of the included studies.

OUTCOMES: We included 163 studies (88 834 women) of moderate overall quality in the narrative synthesis, out of which 96 were included in the meta-analyses. Studies reported on various endometrial receptivity markers evaluated by ultrasound, endometrial biopsy, endometrial fluid aspirate and hysteroscopy in the context of natural conception, IUI and IVF. Associations were identified between clinical pregnancy and various endometrial receptivity markers (endometrial thickness, endometrial pattern, Doppler indices, endometrial wave-like activity and various molecules); however, their poor ability to predict clinical pregnancy prevents them from being used in clinical practice. Results from several modern molecular tests are promising and further data are awaited.

WIDER IMPLICATIONS: The post-test probabilities from our analyses may be used in clinical practice to manage couples' expectations during fertility treatments (IUI and IVF). Conventionally, endometrial receptivity is seen as a dichotomous outcome (present or absent), but we propose that various levels of endometrial receptivity exist within the window of implantation. For instance, different transcriptomic signatures could represent varying levels of endometrial receptivity, which can be linked to different pregnancy outcomes. Many studies reported the means of a particular biomarker in those who achieved a pregnancy compared with those who did not. However, extreme values of a biomarker (as opposite to the means) may have significant prognostic and diagnostic implications that are not captured in the means. Therefore, we suggest reporting the outcomes by categories of biomarker levels rather than reporting means of biomarker levels within clinical outcome groups.

Key words: endometrial receptivity / window of implantation / ultrasound / endometrial biopsy / endometrial fluid aspirate / hysteroscopy / clinical pregnancy / IUI / IVF

Introduction

Early reproductive failure is the most common complication of pregnancy since 70% of conceptions cease development prior to reaching viability (Roberts and Lowe, 1975). More than 50% of pregnancies are lost at pre-clinical stages through implantation failure or biochemical miscarriage (Wilcox *et al.*, 1988; Chard, 1991). Miscarriage then affects 25% of clinical pregnancies (Macklon *et al.*, 2002), with more than 90% of these occurring in the first trimester of pregnancy (Regan and Rai, 2000).

Establishing a successful pregnancy depends upon implantation, a complex process involving interactions between the endometrium and the blastocyst. The window of implantation is described as a narrow time frame with maximal endometrial receptivity, surrounded by a refractory endometrial status (Navot *et al.*, 1986; Tabibzadeh and Babaknia, 1995).

Endometrial receptivity and selectivity are two complementary concepts introduced to describe the endometrium as a biosensor of embryo quality (Macklon and Brosens, 2014). Selectivity is an intrinsic programmed function of the endometrium to recognize and reject embryos with reduced development potential. In contrast, receptivity enables the endometrium to provide an optimal environment for embryo development and placenta formation.

Implantation failure is a consequence of impaired embryo development potential or impaired endometrial selectivity/receptivity, both having a negative effect on the embryo–endometrial cross-talk (Diedrich *et al.*, 2007). It is estimated that embryos account for one-third of implantation failures, while suboptimal endometrial receptivity and altered embryo–endometrial dialogue are responsible for the remaining two-thirds (Edwards, 1994; Simon *et al.*, 1998; Franasiak *et al.*, 2014).

Endometrial receptivity and the characteristics of the window of implantation have been the focus of extensive research for over 80 years, since Rock and Bartlett (1937) described the histological changes of the endometrium around the time of implantation. More recently, microscopy, flow cytometry and molecular advancements have allowed further investigations into the cross-talk between the embryo and the endometrium (Strowitzki *et al.*, 2006). Omics- refer to the application of high-throughput techniques which simultaneously examine changes in different molecular compartments: genomics, transcriptomics, proteomics, metabolomics, etc. The understanding of human endometrial physiology and pathophysiology is being revolutionized by the use of omics (Altmäe *et al.*, 2014).

Despite the indepth understanding of the processes associated with embryo–endometrial cross-talk and implantation, little progress has been achieved for its clinical integration in terms of prognostic tests and treatments for suboptimal endometrial receptivity. The objective of this systematic review was to examine the evidence from observational studies supporting the use of endometrial receptivity markers as prognostic factors for pregnancy outcome in women wishing to conceive in order to aid clinicians in choosing the most useful markers for clinical practice and for informing further research.

Methods

PROSPERO registration and systematic search

The review protocol was registered with PROSPERO (CRD42017077891) on the 1 November 2017 prior to starting the preliminary searches (Craciunas et al., 2017). A comprehensive literature search was then performed in two steps (L.C. and I.G.). An initial search of MEDLINE and Embase was conducted using a very broad search strategy covering keywords and Medical Subject Headings (MeSH) relevant to the review question. This was followed by a more targeted search aiming at identifying additional studies similar to the ones included from the initial search.

Search terms included keywords such as endometrium, uterus, implantation, luteal phase, biopsy, hysteroscopy, ultrasonography, Doppler, thickness, pattern, -omics, natural killer, marker, pregnancy and miscarriage. The search strategy for MEDLINE is published in Supplementary Table SI. Both MEDLINE and Embase were searched for studies published from inception until the date of the final search (26 February 2018) with no restrictions. The 'Similar articles' function in PubMed and 'Related articles' function in Google Scholar were used to identify further relevant publications. The reference lists of all relevant publications were screened to complete the literature search.

Study selection, data extraction and quality assessment

Primary observational studies that reported original data regarding potential markers of endometrial receptivity were included in the present systematic review if they provided clinical outcomes from either natural conceptions or fertility treatments (IUI or IVF). Interventional studies, commentaries, narrative reviews and letters were excluded. Case reports, case series, cohort studies with fewer than 15 participants and studies published as abstracts only were also excluded.

We only included studies that measured the markers of endometrial receptivity prior to pregnancy events (implantation failure, miscarriage, clinical pregnancy, live birth) to avoid the potential bias secondary to changes caused by the pregnancy event itself. Studies were deemed eligible irrespective of the country of origin, authors or affiliations, language or year of publication.

One author (L.C.) screened the titles and abstracts to compile a list of potentially eligible studies. The full manuscripts were assessed and data was extracted with pre-defined spreadsheets. A second author (I.G.) verified extracted data against the full manuscripts. Any disagreement was resolved through discussion, with a plan to involve a third author (J.C.) if the disagreement persisted.

The Newcastle–Ottawa Scale (Wells et al.) for observational studies was employed to assess the selection of cohorts, the comparability of study design and the adequacy of outcome assessment and follow-up. The scale uses a stars system to award the highest quality studies up to nine stars.

Primary and secondary outcomes

The included studies reported various endometrial receptivity markers evaluated by ultrasound imaging, endometrial biopsy, endometrial fluid aspirate or hysteroscopy. The markers were described separately in the results section.

Association and accuracy data were provided in relation to clinical pregnancy (defined as intrauterine pregnancy diagnosed by the presence of a gestational sac on ultrasound scan), miscarriage (defined as clinical pregnancy loss before 24 weeks of gestation) or live birth (defined as a live born baby after 24 weeks of gestation).

Data analysis and presentation

The pooled outcome was calculated as a mean difference (MD) for markers of endometrial receptivity reported as means between study groups. If the SD was not provided, it was calculated according to the guidelines of the Cochrane Collaboration (Higgins and Green, 2011) assuming that both groups had the same variance. The Inverse Variance method was used for the calculation of MD with 95% CI under the random-effects model (DeMets, 1987) to account for the clinical heterogeneity between the study populations. Risk ratio (RR) with 95% CI was calculated for markers of endometrial receptivity reported as dichotomous variables (or relative to a cut-off value) using the Mantel–Haenszel method under the random-effects model.

Heterogeneity was explored using the χ^2 test, with significance set at $P < 0.05$. I^2 was used to quantify heterogeneity (Higgins and Thompson, 2002), with a maximum value of 40% identifying low heterogeneity, while >40% identified substantial heterogeneity. Forest plots were used for the graphical display of the results from the association meta-analyses. The square around the estimate is proportional to the weight used in meta-analysis and the horizontal line represents the 95% CI. Review Manager (RevMan) software (Version 5.3, The Cochrane Collaboration, 2014) was used for the calculation of MD and RR.

For tests with sufficient data, we plotted estimates of sensitivities and specificities from individual studies on summary receiver operating characteristics space for visual examination of heterogeneity. We used STATA statistical package to meta-analyse a pair of sensitivity and specificity from each included study by using the hierarchical summary receiver operating characteristics approach (Rutter and Gatsonis, 2001; Macaskill, 2004). This approach estimates the position and shape of the summary receiver operating characteristics curve and takes into account both within and between study variations. We fitted a two-level mixed logistic regression model, with independent binomial distributions for the true positives and true negatives conditional on the sensitivity and specificity in each study, and a bivariate normal model transforming sensitivity and specificity between studies. When all the parameters of the hierarchical summary receiver operating characteristics model could not be estimated owing to a limited number of studies, we simplified it by assuming a symmetrical shape for the curve. For meta-analysis of studies that used the same cut-off values, we used parameter estimates from the models to derive summary operating points (that is, summary sensitivities and specificities), with 95% confidence regions, and summary likelihood ratios.

Endometrial receptivity markers were grouped and reported based on the investigation that led to their measurement (ultrasound, endometrial biopsy, endometrial fluid aspirate and hysteroscopy). The methods of conception (natural, IUI and IVF with fresh or non-fresh embryo transfers) were considered as sub-groups according to the published protocol.

Accuracy measures (sensitivity, specificity, likelihood ratios for positive and negative test results, post-test probabilities) were presented in three different tables for IUI, IVF with fresh embryo transfer and IVF with non-fresh (frozen–thawed or donated embryos with or without endometrial preparation) embryo transfer, respectively. Pooled measures were presented if sufficient data were available for meta-analysis. Accuracy measures from the largest studies reporting individual endometrial receptivity markers and cut-offs were presented if data were insufficient for meta-analysis. Post-test probabilities were calculated using the likelihood ratios and a pre-test probability was defined by the overall clinical pregnancy rate of the largest study reporting on women undergoing IUI, IVF with fresh and non-fresh embryo transfer, respectively. In the absence of a gold standard diagnostic test for endometrial receptivity, we considered

clinical pregnancy as an outcome to reflect the presence of receptive endometrium.

Results

The literature search identified 36 145 articles after removal of duplicates. Titles and abstracts were screened to exclude 35 791 articles for not being relevant to the question of the present review. The full text of the remaining 354 articles was assessed for eligibility. Out of these, 191 were excluded. We included 163 studies (88 834 women) in the narrative synthesis, 96 out of which were included in the meta-analyses. Figure 1 displays the flow diagram for the selection of the studies. Figure 2 displays the summary of the main results.

The vast majority of the included studies reported on markers of endometrial receptivity in the context of IVF (138/163, 85%) and evaluated by ultrasound (120/163, 74%). The studies were conducted in 36 different countries and included a median of 124 women (range: 17–21 752). The characteristics of included studies are given in Supplementary Table SII.

The overall quality of the studies assessed using The Newcastle–Ottawa Scale was moderate. High scores were obtained for participants' selection and follow up of reported outcomes. Low scores were obtained for cohorts' comparability as confounding factors were very rarely accounted for. Few studies reported on live birth as a reproductive outcome, while clinical pregnancy was the most frequently reported outcome during follow up.

The largest IUI study (Khalil *et al.*, 2001) assessing endometrial receptivity markers included 893 women (2473 cycles) and reported an overall clinical pregnancy rate of 11.9%. The largest fresh embryo transfer IVF study (Gallos *et al.*, 2018) included 21 752 women (25 433 cycles) and reported a clinical pregnancy rate of 39.9%. For IVF with non-fresh embryo transfer, the largest study (Bu *et al.*, 2016) included 2997 women (2997 cycles) and reported a clinical pregnancy rate of 40.6%. These pre-test probabilities were used to calculate the post-test probabilities for IUI (Table I), IVF with fresh embryo transfer (Table II) and IVF with non-fresh embryo transfer (Table III), respectively.

Endometrial receptivity markers evaluated by ultrasound

Endometrial thickness

Studies measured the endometrial thickness for women undergoing IUI and IVF with fresh or non-fresh embryo transfer. Endometrial thickness was reported at various time points in relation to IUI (during ovarian stimulation, on the day of hCG injection, on the day of IUI), fresh embryo transfer (mid-luteal phase in the cycle preceding the IVF cycle, day of hCG injection, day after hCG injection, day of oocyte retrieval, day of embryo transfer) and non-fresh embryo

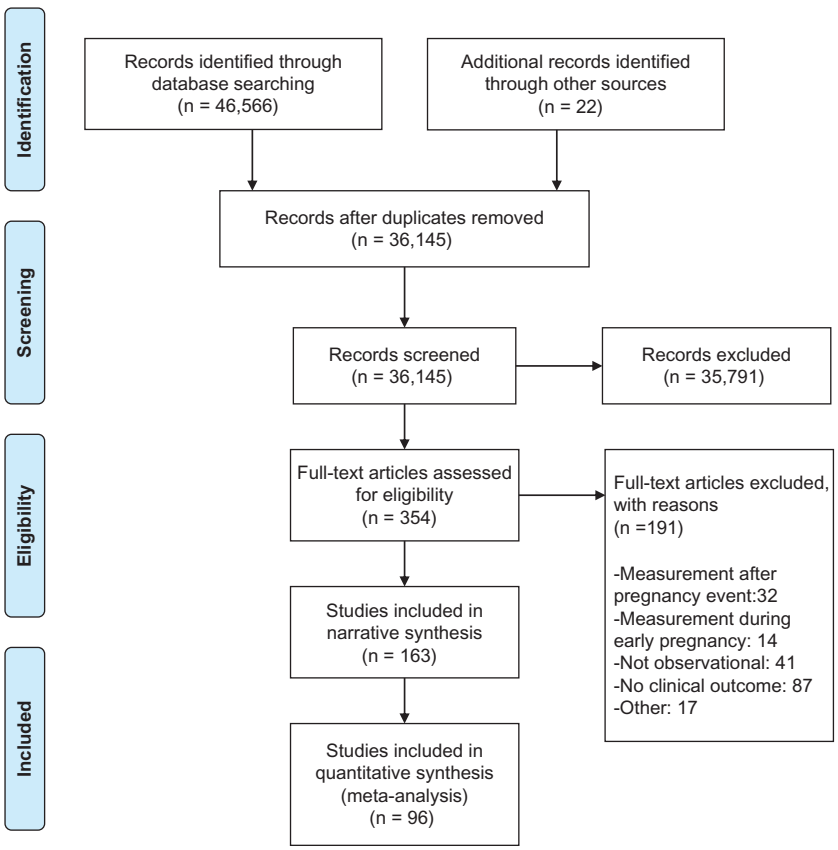

Figure 1 PRISMA flow diagram of search and selection strategy.

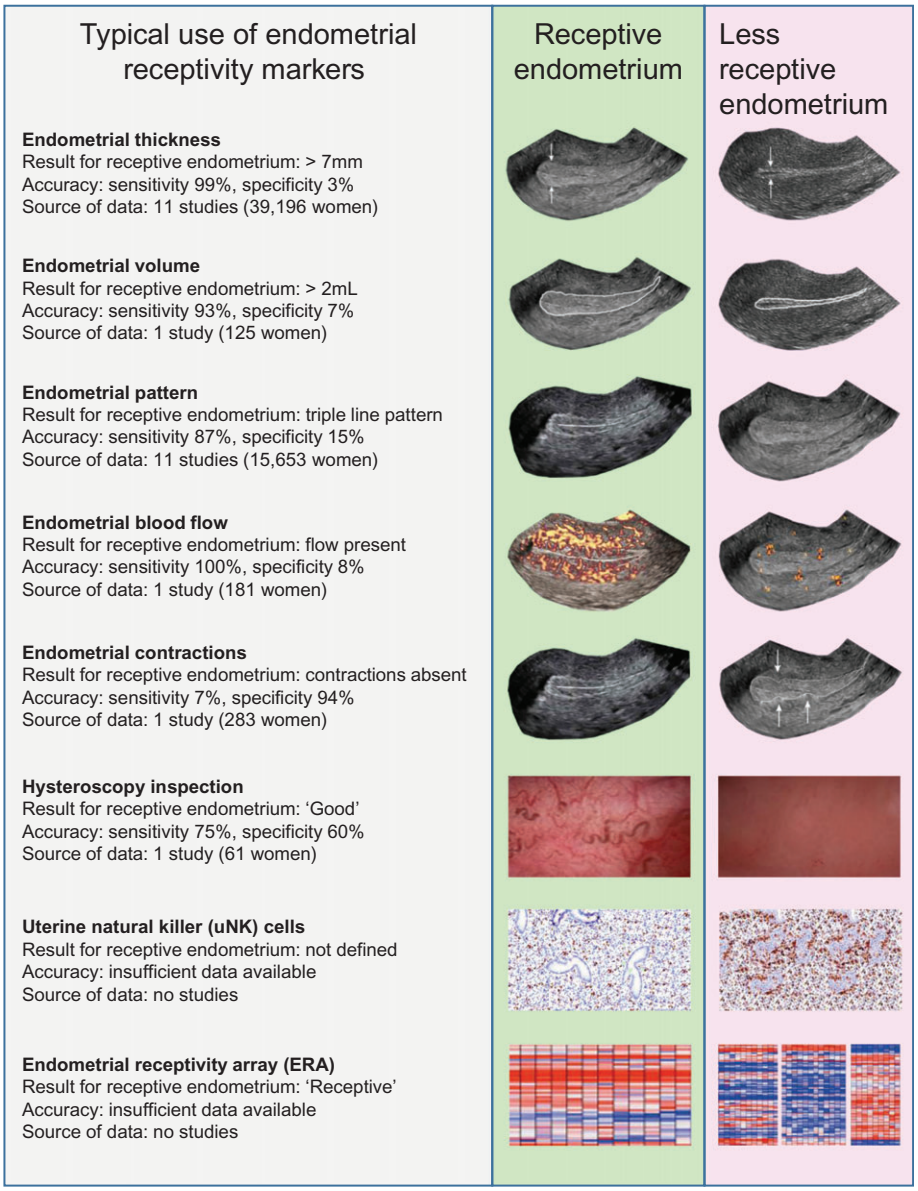

Figure 2 Summary of the main findings. The prognostic accuracy of endometrial receptivity markers for clinical pregnancy.

transfer (day of LH surge in natural cycle, day of commencing progesterone, day of embryo transfer).

Association analyses (using means): Sufficient data were available to perform meta-analysis of studies reporting the mean endometrial thickness between clinically pregnant and not pregnant women in the context of IUI and IVF with fresh and non-fresh embryo transfer.

Ten studies reported the mean endometrial thickness for women achieving clinical pregnancy versus women without a clinical pregnancy after IUI. The endometrial thickness measured on the day of the hCG injection was higher in the clinical pregnancy group compared to no clinical pregnancy group (MD, 1.16; 95% CI: 0.29–2.03; $z = 2.62$; $P < 0.0009$; six studies; 1635 cycles; substantial heterogeneity: $I^2 = 97\%$, Supplementary Fig. S1). No significant difference was observed in the endometrial thickness measured on the day of IUI between the groups (MD, 0.54; 95% CI: −0.3 to 2.5; $z = 1.58$; $P = 0.11$; four studies; 556 cycles; low heterogeneity: $I^2 = 36\%$, Supplementary Fig. S1).

Thirty-four studies reported the mean endometrial thickness for women achieving clinical pregnancy versus women without a clinical pregnancy after IVF with fresh embryo transfer. Endometrial thickness measured on the day of hCG injection was higher in the group of women who achieved a clinical pregnancy compared to women who did not (MD, 0.43; 95% CI: 0.21–0.64; $z = 3.87$; $P < 0.0001$; 20 studies; 18 690 cycles; substantial heterogeneity: $I^2 = 83\%$, Supplementary Fig. S2). No difference was observed in the mean endometrial thickness between the clinically pregnant and not pregnant groups on the day of oocyte retrieval (MD, −0.5; 95% CI: −1.29 to 0.3; $z = 1.23$; $P = 0.22$; three studies; 252 cycles; no heterogeneity: $I^2 = 0\%$,

Table I Accuracy measures for endometrial receptivity markers based on their ability to predict clinical pregnancy (CP) following IUI.

Studies (cycles)	Cut-off for positive test (should identify receptive endometrium)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	Post-test probabilities for CP (95% CI) Based on a pre-test probability of 11.9%	
						After test if positive (%)	After test if negative (%)
Endometrial receptivity markers evaluated by ultrasound							
Endometrial thickness on the day of hCG injection to predict CP after IUI							
1 (562)	>3 mm	100 (96.03–100)	0.42 (0.05–1.53)	1 (1–1.01)	0	11.9 (11.9–12)	0
1 (562)	>4 mm	96.7 (90.67–99.31)	4.88 (3.12–7.24)	1.02 (0.97–1.06)	0.68 (0.21–2.2)	12.1 (11.6–12.5)	8.4 (2.8–22.9)
1 (562)	>5 mm	87.91 (79.4–93.81)	12.53 (9.67–15.86)	1.01 (0.92–1.09)	0.96 (0.53–1.76)	12 (11.1–12.8)	11.5 (6.7–19.2)
4 (1569)	>6 mm	91.92 (75.59–97.66)	13.75 (6.9–25.53)	1.07 (1–1.13)	0.59 (0.28–1.24)	12.6 (11.9–13.2)	7.4 (3.6–14.3)
1 (562)	>7 mm	52.75 (42–63.31)	47.98 (43.39–52.6)	1.01 (0.82–1.25)	0.98 (0.78–1.25)	12 (10–14.4)	11.7 (9.5–14.4)
1 (562)	>8 mm	30.77 (21.51–41.32)	65.61 (61.12–69.89)	0.89 (0.64–1.25)	1.06 (0.91–1.23)	10.7 (8–14.4)	12.5 (10.9–14.2)
1 (562)	>9 mm	21.98 (13.97–31.88)	79.83 (75.92–83.36)	1.09 (0.71–1.67)	0.98 (0.87–1.1)	12.8 (8.8–18.4)	11.7 (10.5–12.9)
1 (562)	>10 mm	12.09 (6.19–20.6)	90.02 (86.95–92.58)	1.21 (0.65–2.24)	0.98 (0.9–1.06)	14 (8.1–23.2)	11.7 (10.8–12.5)
1 (562)	>11 mm	5.49 (1.81–12.36)	94.06 (91.52–96.01)	0.92 (0.37–2.33)	1 (0.95–1.06)	11.1 (4.8–23.9)	11.9 (11.4–12.5)
1 (562)	>12 mm	1.1 (0.03–5.97)	98.3 (96.68–99.26)	0.65 (0.08–5.11)	1.01 (0.98–1.03)	8.1 (1.1–40.8)	12 (11.7–12.2)
Endometrial thickness on other days to predict CP after IUI							
1 (1368)	>6 mm on Day 10 of cycle	58.7 (51.22–65.89)	38.85 (36.06–41.69)	0.96 (0.84–1.09)	1.06 (0.88–1.28)	11.5 (10.2–12.8)	12.5 (10.6–14.7)
1 (100)	>7 mm on Day of IUI	41.67 (25.51–59.24)	35.94 (24.32–48.9)	0.65 (0.42–1)	1.62 (1.06–2.49)	8.1 (5.4–11.9)	18 (12.5–25.2)
1 (100)	>14 mm on Day of IUI	2.78 (0.07–14.53)	100 (94.4–100)	N/A	0.97 (0.92–1.03)	N/A	11.6 (11.1–12.2)
Endometrial pattern at various timings to predict CP after IUI							
1 (1371)	Triple line on Day 10 of cycle	82.07 (75.75–87.32)	17.61 (15.48–19.9)	1 (0.93–1.07)	1.02 (0.73–1.42)	11.9 (11.2–12.6)	12.1 (9–16.1)
5 (1525)	Triple line on day of hCG	84.36 (68.02–93.19)	27.24 (17.49–39.81)	1.16 (1.07–1.26)	0.57 (0.35–0.93)	13.5 (12.6–14.5)	7.1 (4.5–11.2)
1 (241)	Triple line on day of IUI	100 (92.75–100)	10.94 (6.9–16.23)	1.12 (1.07–1.18)	0	13.1 (12.6–13.7)	0
Other ultrasound markers on the day of IUI to predict CP after IUI							
1 (104)	Endometrial volume >2 mL	78.57 (49.2–95.34)	56.67 (45.8–67.08)	1.81 (1.26–2.6)	0.38 (0.14–1.05)	19.6 (14.5–26)	4.9 (1.9–12.4)
1 (105)	Uterine artery diastolic notch: absent	0 (0–16.11)	91.67 (83.58–96.58)	0	1.09 (1.02–1.16)	0	12.8 (12.1–13.5)
1 (241)	<4 contractions/min	61.22 (46.24–74.8)	57.29 (49.97–64.39)	1.43 (1.09–1.89)	0.68 (0.47–0.98)	16.2 (12.8–20.3)	8.4 (6–11.7)
Endometrial receptivity markers evaluated by endometrial fluid aspirate							
1 (50)	Activin A >0.04 ng/mL	76 (56.6–88.5)	100 (86.7–100)	19.8	0.25	72.8	3.3
1 (71)	Urocortin >0.321 ug/L,	60.7 (40.6–78.5)	97.7 (87.7–99.6)	26.11	0.4	77.9	5.1

LR+ = likelihood ratio of a positive test result; LR− = likelihood ratio of a negative test result.

Supplementary Fig. S2). Endometrial thickness measured on the day of fresh embryo transfer was higher in the clinical pregnancy group compared to the no pregnancy group (MD, 0.26; 95% CI, 0.02 to 0.49; $z = 2.16$; $P < 0.03$; 13 studies; 3695 cycles; substantial heterogeneity: $I^2 = 58\%$, Supplementary Fig. S2).

Eleven studies reported the mean endometrial thickness for women achieving clinical pregnancy versus women without a clinical pregnancy after IVF with non-fresh embryo transfer. Endometrial thickness measured on the day of commencing progesterone was higher in the clinical pregnancy group compared to the no clinical pregnancy group (MD, 0.46; 95% CI: 0.04–0.87; $z = 2.17$; $P < 0.03$; three studies; 2054 cycles; substantial heterogeneity: $I^2 = 91\%$, Supplementary Fig. S3). Endometrial thickness measured on the day of the non-fresh embryo transfer was similar between the groups (MD, 0.19; 95% CI: −0.57 to 0.96; $z = 0.49$; $P = 0.63$; six studies; 366 cycles; substantial heterogeneity: $I^2 = 74\%$, Supplementary Fig. S3).

Association analyses (using cut-offs): Sufficient data were available to perform meta-analysis of studies reporting various cut-offs for endometrial thickness and the corresponding clinical pregnancy rates in the context of IUI and IVF with fresh embryo transfer.

Four studies contributed data for association analyses between endometrial thicknesses cut-offs ranging from 3 to 12 mm on the day

Table II Accuracy measures for endometrial receptivity markers based on their ability to predict clinical pregnancy (CP) following IVF with fresh embryo transfer (ET).

Studies (cycles)	Cut-off for positive test (should identify receptive endometrium)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	Post-test probabilities for CP (95% CI) Based on a pre-test probability of 39.9%	
						After test if positive (%)	After test if negative (%)
Endometrial receptivity markers evaluated by ultrasound							
Endometrial thickness on the day of hCG injection to predict CP after fresh ET							
4 (28 868)	>6 mm	99.63 (98.75–99.89)	0.98 (0.32–3)	1 (1–1.01)	0.38 (0.18–0.77)	39.9 (39.9–40.1)	20.1 (10.7–33.8)
11 (39 196)	>7 mm	98.82 (98.2–99.23)	2.73 (1.72–4.31)	1.01 (1–1.02)	0.43 (0.35–0.53)	40.1 (39.9–40.4)	22.2 (18.9–26)
10 (37 238)	>8 mm	94.77 (91.75–96.72)	10.16 (5.51–17.98)	1.05 (1.01–1.1)	0.51 (0.42–0.64)	41.1 (40.1–42.2)	25.3 (21.8–29.8)
7 (35 733)	>9 mm	87.79 (84.07–90.74)	17.75 (12.75–24.16)	1.07 (1.03–1.1)	0.69 (0.64–0.74)	41.5 (40.6–42.2)	31.4 (29.8–32.9)
9 (35 568)	>10 mm	68.29 (57.68–77.28)	41.1 (29.45–53.84)	1.16 (1.07–1.25)	0.77 (0.72–0.83)	43.5 (41.5–45.4)	33.8 (32.3–35.5)
6 (34 776)	>11 mm	56.61 (49.42–63.53)	53.72 (43.7–63.44)	1.22 (1.1–1.36)	0.81 (0.76–0.86)	44.7 (42.2–47.4)	35 (33.5–36.3)
9 (35 449)	>12 mm	30.19 (20.41–42.18)	78.92 (65.46–88.09)	1.43 (1.17–1.76)	0.88 (0.85–0.92)	48.7 (43.7–53.9)	36.9 (36.1–37.9)
6 (34 776)	>13 mm	23.77 (17.76–31.03)	82.62 (74.11–88.76)	1.37 (1.15–1.63)	0.92 (0.9–0.95)	47.6 (43.3–62)	37.9 (37.4–38.7)
15 (42 163)	>14 mm	9.08 (6.28–12.95)	92.78 (89.78–94.95)	1.26 (1.09–1.45)	0.98 (0.97–1)	45.5 (42–49)	39.4 (39.2–39.9)
1 (25 433)	>15 mm	9.4 (8.84–9.98)	92.14 (91.7–92.56)	1.2 (1.1–1.3)	0.98 (0.98–0.99)	44.3 (42.2–46.3)	39.4 (39.4–39.7)
1 (25 433)	>16 mm	5.11 (4.69–5.55)	95.59 (95.25–95.91)	1.16 (1.04–1.29)	0.99 (0.99–1)	43.5 (40.8–46.1)	39.7 (39.7–39.9)
1 (25 433)	>17 mm	2.68 (2.37–3.01)	97.79 (97.55–98.02)	1.21 (1.04–1.42)	1 (0.99–1)	44.5 (40.8–48.5)	39.9 (39.7–39.9)
Endometrial thickness on the day of ET to predict CP after fresh ET							
1 (1228)	>7 mm	99.75 (98.62–99.99)	0.36 (0.07–1.06)	1 (0.99–1.01)	0.68 (0.07–6.56)	39.9 (39.7–40.1)	31.1 (4.4–81.3)
1 (1228)	>8 mm	98.76 (97.12–99.59)	2.54 (1.58–3.86)	1.01 (1–1.03)	0.49 (0.19–1.29)	40.1 (39.9–40.6)	24.5 (11.2–46.1)
1 (1228)	>9 mm	91.29 (88.1–93.86)	11.14 (9.07–13.48)	1.03 (0.99–1.07)	0.78 (0.54–1.13)	40.6 (39.7–41.5)	34.1 (26.4–42.9)
1 (1228)	>10 mm	76.62 (72.17–80.67)	28.81 (25.74–32.03)	1.08 (1–1.15)	0.81 (0.66–1)	41.8 (39.9–43.3)	35 (30.5–39.9)
1 (1228)	>11 mm	53.48 (48.47–58.44)	56.17 (52.71–59.59)	1.22 (1.08–1.38)	0.83 (0.73–0.93)	44.7 (41.8–47.8)	35.5 (32.6–38.2)
1 (1228)	>12 mm	34.08 (29.45–38.94)	74.46 (71.34–77.4)	1.33 (1.12–1.60)	0.89 (0.82–0.96)	46.9 (42.6–51.5)	37.1 (35.2–38.9)
1 (1228)	>13 mm	24.36 (19.7–29.51)	88.01 (85.6–90.15)	2.03 (1.55–2.66)	0.86 (0.8–0.92)	57.4 (50.7–63.8)	36.3 (34.7–37.9)
1 (1228)	>14 mm	7.96 (5.51–11.5)	94.43 (92.64–95.89)	1.43 (0.93–2.21)	0.97 (0.94–1.01)	48.7 (38.2–59.5)	39.2 (38.4–40.1)
1 (1228)	>15 mm	3.23 (1.73–5.47)	98.06 (96.87–98.89)	1.67 (0.81–3.44)	0.99 (0.97–1.01)	52.6 (35–69.5)	39.7 (39.2–40.1)
1 (1228)	>16 mm	0.75 (0.15–2.17)	99.39 (98.59–99.8)	1.23 (0.3–5.13)	1 (0.99–1.01)	45 (16.6–77.3)	39.9 (39.7–40.1)
Endometrial pattern at various timings to predict CP after fresh ET							
11 (15 653)	Triple line on day of hCG	86.93 (81.02–91.2)	14.83 (7.93–26.05)	1.02 (0.97–1.07)	0.88 (0.69–1.13)	40.4 (39.2–41.5)	36.9 (31.4–42.9)
6 (778)	Triple line on day of ET	69.59 (34.82–90.74)	35.43 (16.63–60.15)	1.08 (0.92–1.26)	0.86 (0.55–1.34)	41.8 (37.9–45.5)	36.3 (26.7–47.1)
Endometrial volume at various timings to predict CP after fresh ET							
1 (103)	>2 mL on day of hCG	93.33 (81.73–98.6)	6.9 (1.91–16.73)	1 (0.9–1.11)	0.97 (0.23–4.1)	39.9 (37.4–42.4)	39.2 (13.2–73.1)
1 (103)	>4 mL on day of hCG	68.89 (53.35–81.83)	44.83 (31.74–58.46)	1.25 (0.92–1.69)	0.69 (0.41–1.17)	45.4 (37.9–52.9)	31.4 (21.4–43.7)
1 (125)	>2 mL on day of ET	93.5	22.2	1.2	0.29	44.3	16.1
1 (125)	>2.5 mL on day of ET	90.3	35.8	1.41	0.27	48.3	15.2
Uterine artery PI at various timings to predict CP after fresh ET							
1 (112)	<3 on day of hCG	100 (90.51–100)	2.67 (0.32–9.30)	1.03 (0.99–1.07)	0	40.6 (39.7–41.5)	0
1 (174)	<3 on day of ET	91.94 (82.17–97.33)	26.79 (18.86–35.98)	1.26 (1.1–1.44)	0.3 (0.12–0.74)	45.5 (42.2–48.9)	16.6 (7.4–32.9)
Uterine artery protodiastolic notch at various timings to predict CP after fresh ET							
1 (96)	Absent mid-luteal before ET cycle	31.03 (15.28–50.83)	71.64 (59.31–81.99)	1.09 (0.56–2.12)	0.96 (0.72–1.28)	42 (27.1–58.5)	38.9 (32.3–45.9)
1 (112)	Absent on day of hCG	78.38 (61.79–90.17)	42.67 (31.31–54.62)	1.37 (1.06–1.77)	0.51 (0.26–0.99)	47.6 (41.3–54)	25.3 (14.7–39.7)
1 (178)	Absent on day of ET	7.46 (2.47–16.56)	99.1 (95.08–99.98)	8.28 (0.99–69.4)	0.93 (0.87–1)	84.6 (39.7–97.9)	38.2 (36.6–39.9)

Continued

Table II *Continued*

Studies (cycles)	Cut-off for positive test (should identify receptive endometrium)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	Post-test probabilities for CP (95% CI) Based on a pre-test probability of 39.9%	
						After test if positive (%)	After test if negative (%)
Endometrial blood flow at various timings to predict CP after fresh ET							
1 (96)	Present mid-luteal before ET cycle	79.31 (60.28–92.01)	55.22 (42.58–67.4)	1.77 (1.28–2.45)	0.37 (0.18–0.79)	54 (45.9–61.9)	19.7 (10.7–34.4)
1 (181)	Present on day of hCG	100 (94.87–100)	8.11 (3.77–14.83)	1.09 (1.03–1.15)	0	42 (40.6–43.3)	0
1 (623)	Present on day of ET	36.16 (29.08–43.70)	84.3 (80.59–87.56)	2.3 (1.72–3.08)	0.76 (0.67–0.85)	60.4 (53.3–67.2)	33.5 (30.8–36.1)
Uterine contractions on the day of ET to predict CP after fresh ET							
1 (283)	Absent	6.72 (2.95–12.82)	93.9 (89.07–97.04)	1.1 (0.45–2.71)	0.99 (0.93–1.06)	42.2 (23–64.3)	39.7 (38.2–41.3)
1 (220)	<3 contractions/min	39.44 (28.03–51.75)	83.22 (76.24–88.84)	2.35 (1.48–3.72)	0.73 (0.6–0.89)	60.9 (49.6–71.2)	32.6 (28.5–37.1)
1 (220)	<4 contractions/min	71.83 (59.9–81.87)	65.1 (56.87–72.72)	2.06 (1.58–2.68)	0.43 (0.29–0.64)	57.8 (51.2–64)	22.2 (16.1–29.8)
1 (220)	<5 contractions/min	85.92 (75.62–93.03)	42.95 (34.88–51.31)	1.51 (1.27–1.78)	0.33 (0.18–0.6)	50.1 (45.7–54.2)	18 (10.7–28.5)
Endometrial receptivity markers evaluated by endometrial biopsy							
1 (69)	BLC6 ≤1.4	55 (31.53–76.94)	87.76 (75.23–95.37)	4.49 (1.92–10.49)	0.51 (0.31–0.84)	74.9 (56–87.4)	25.3 (17.1–35.8)
1 (52)	α-Inhibin >1.26	64 (47–78)	68 (46–85)	2.02 (0.99–4.10)	0.53 (0.31–0.92)	57.3 (39.7–73.1)	26 (17.1–37.9)
1 (52)	β-Glycan >1.22	67 (50–80)	74 (51–88)	2.53 (1.15–5.58)	0.45 (0.26–0.79)	62.7 (43.3–78.7)	23 (14.7–34.4)
1 (66)	Luminal αvβ3 >0.7	85.71 (67.33–95.97)	28.95 (15.42–45.9)	1.21 (0.94–1.55)	0.49 (0.18–1.39)	44.5 (38.4–50.7)	24.5 (10.7–48)
1 (56)	L-selectin ligand: high	68.18 (45.13–86.14)	61.76 (43.56–77.83)	1.78 (1.07–2.98)	0.52 (0.26–1)	54.2 (41.5–66.4)	25.7 (14.7–39.9)
1 (122)	Aromatase P450 <8.3	93.75 (79.19–99.23)	21.11 (13.21–30.99)	1.19 (1.03–1.37)	0.3 (0.07–1.2)	44.1 (40.6–47.6)	16.6 (4.4–44.3)
1 (49)	Glandular VEGF-A >6	60 (26.24–87.84)	87.18 (72.57–95.7)	4.68 (1.79–12.25)	0.46 (0.21–0.99)	75.7 (54.3–89.1)	23.4 (12.2–39.7)
Endometrial receptivity markers evaluated by endometrial fluid aspirate							
1 (109)	hDP 200 <100 mU/mg	92.86 (66.13–99.82)	17.89 (10.78–27.1)	1.13 (0.95–1.34)	0.4 (0.06–2.77)	42.9 (38.7–47.1)	21 (3.8–64.8)
1 (109)	hDP 200 <1000 mU/mg	57.14 (28.86–82.34)	69.47 (59.18–78.51)	1.87 (1.08–3.23)	0.62 (0.33–1.15)	55.4 (41.8–68.2)	29.2 (18–43.3)
1 (109)	hDP 200 <10000 mU/mg	28.57 (8.39–58.1)	95.79 (89.57–98.84)	6.79 (1.91–24.1)	0.75 (0.53–1.04)	81.8 (55.9–94.1)	33.2 (26–40.8)
1 (133)	IL-18 <12.5 pg/mL	85.71 (71.46–94.57)	35.16 (25.44–45.88)	1.32 (1.09–1.61)	0.41 (0.18–0.9)	46.7 (42–51.7)	21.4 (10.7–37.4)
Endometrial receptivity markers evaluated by hysteroscopy							
1 (61)	'Good' endometrium	75 (47.62–92.73)	60 (44.33–74.3)	1.88 (1.19–2.96)	0.42 (0.17–1.01)	55.5 (44.1–66.3)	21.8 (10.1–40.1)
1 (75)	Endometrial blood flow >29 mL/min/100 g	71.43 (47.82–88.72)	61.11 (46.88–74.08)	1.84 (1.19–2.82)	0.47 (0.23–0.95)	55 (44.1–65.2)	23.8 (13.2–38.7)

LR+ = likelihood ratio of a positive test result; LR− = likelihood ratio of a negative test result.

of the hCG injection and clinical pregnancy following IUI. The most used cut-off was 6 mm. There was no difference in clinical pregnancy after IUI between women who had an endometrial thickness higher than 6 mm compared to women with a thinner than 6 mm endometrium on the day of hCG injection (RR, 1.19; 95% CI: 0.82–1.71; $z = 0.92$; $P = 0.36$; four studies; 1569 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S4). No difference was observed for any of the other endometrial thickness cut-offs (Supplementary Fig. S4).

Nineteen studies contributed data for association analyses between endometrial thicknesses cut-offs ranging from 6 to 17 mm on the day of the hCG injection and clinical pregnancy following IVF with fresh embryo transfer. There was a positive association between clinical pregnancy and higher endometrial thickness for every cut-off. The measure of association decreased gradually from the 6 mm cut-off (RR, 1.85; 95% CI: 1.28–2.67; $z = 3.28$; $P < 0.001$; four studies; 30 361 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S5) to the 17 mm cut-off (RR, 1.14; 95% CI, 1.06 to 1.24; $z = 3.38$; $P < 0.0007$; five studies; 30 793 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S5). Figure 3 summarizes the pooled outcomes shown in Supplementary Fig. S5.

Accuracy analyses (using cut-offs): Sufficient data were available to perform test accuracy meta-analysis of studies reporting various cut-offs for endometrial thickness and the corresponding clinical pregnancy rate in the context of IUI and IVF with fresh embryo transfer.

Four studies provided clinical pregnancy data in relation to the 6 mm cut-off for endometrial thickness as measured on the day of hCG injection in women undergoing IUI. The sensitivity was 91.9% and the specificity was 13.8% (four studies, 1569 cycles).

Table III Accuracy measures for endometrial receptivity markers based on their ability to predict clinical pregnancy (CP) following IVF with non-fresh embryo transfer (ET).

Studies (cycles)	Cut-off for positive test (should identify receptive endometrium)	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	Post-test probabilities for CP (95% CI) Based on a pre-test probability of 40.6%	
						After test if positive (%)	After test if negative (%)
Endometrial receptivity markers evaluated by ultrasound							
Endometrial thickness on the day of progesterone start to predict CP after non-fresh ET							
1 (1512)	>6 mm	99.21 (98.44–99.66)	2.98 (1.68–4.87)	1.02 (1.02–1.04)	0.27 (0.11–0.62)	41.1 (41.1–41.5)	15.6 (7–29.8)
1 (1512)	>7 mm	96.13 (94.75–97.24)	6.16 (4.23–8.63)	1.02 (1–1.05)	0.63 (0.4–0.99)	41.1 (40.6–41.8)	30.1 (21.5–40.4)
1 (1512)	>8 mm	80.67 (78.1–83.07)	24.65 (20.94–28.66)	1.07 (1.01–1.14)	0.78 (0.64–0.96)	42.2 (40.8–43.8)	34.8 (30.4–39.6)
1 (1512)	>9 mm	41.53 (38.46–44.64)	63.22 (58.84–67.45)	1.13 (0.99–1.29)	0.92 (0.85–1.01)	43.6 (40.4–46.9)	38.6 (36.7–40.8)
1 (1512)	>10 mm	22 (19.48–24.69)	82.11 (78.47–85.36)	1.23 (0.99–1.53)	0.95 (0.9–1)	45.7 (40.4–51.1)	39.4 (38.1–40.6)
1 (1512)	>11 mm	9.81 (8.05–11.82)	91.85 (89.1–94.09)	1.2 (0.85–1.7)	0.98 (0.95–1.01)	45.1 (36.7–53.7)	40.1 (39.4–40.8)
1 (1512)	>12 mm	5.15 (3.87–6.7)	95.83 (93.69–97.4)	1.23 (0.75–2.03)	0.99 (0.97–1.01)	45.7 (33.9–58.1)	40.4 (39.9–40.8)
1 (1512)	>13 mm	2.68 (1.77–3.87)	97.42 (95.62–98.62)	1.04 (0.54–1.99)	1 (0.98–1.02)	41.5 (27–57.6)	40.6 (40.1–41.1)
1 (1512)	>14 mm	0.89 (0.41–1.69)	99.2 (97.98–99.78)	1.12 (0.35–3.62)	1 (0.99–1.01)	43.4 (19.3–71.2)	40.6 (40.4–40.8)
Endometrial thickness on the day of ET to predict CP after non-fresh ET							
1 (737)	>6 mm	92.76 (88.51–95.81)	7.36 (5.26–9.97)	1 (0.96–1.05)	0.98 (0.56–1.73)	40.6 (39.6–41.8)	40.1 (27.7–54.2)
1 (236)	>7 mm	89.29 (82.03–94.34)	9.68 (5.1–16.29)	0.99 (0.91–1.08)	1.11 (0.52–2.36)	40.4 (38.3–42.5)	43.1 (26.2–61.7)
1 (2997)	>8 mm	89.49 (87.63–91.16)	14.33 (12.74–16.05)	1.04 (1.02–1.07)	0.73 (0.6–0.89)	41.5 (41.1–42.2)	33.3 (29.1–37.8)
1 (737)	>9 mm	33.94 (27.72–40.59)	69.38 (65.20–73.33)	1.11 (0.88–1.39)	0.95 (0.85–1.06)	43.1 (37.6–48.7)	39.4 (36.7–42)
1 (737)	>10 mm	14.93 (10.51–20.33)	80.43 (76.74–83.76)	0.76 (0.53–1.09)	1.06 (0.99–1.13)	34.2 (26.6–42.7)	42 (40.4–43.6)
1 (236)	>11 mm	14.29 (8.39–22.16)	81.45 (73.48–87.86)	0.77 (0.43–1.38)	1.05 (0.94–1.18)	34.5 (22.7–48.5)	41.8 (39.1–44.6)
1 (236)	>12 mm	6.25 (2.55–12.45)	87.9 (80.83–93.07)	0.52 (0.22–1.22)	1.07 (0.98–1.16)	26.2 (13.1–45.5)	42.2 (40.1–44.2)
1 (2997)	>14 mm	8.87 (7.33–10.61)	92.69 (91.38–93.86)	1.21 (0.95–1.55)	0.98 (0.96–1)	45.3 (39.4–51.4)	40.1 (39.6–40.6)
Endometrial pattern at various timings to predict CP after non-fresh ET							
1 (100)	Triple line on day of ovulation	100 (89.72–100)	9.09 (3.41–18.74)	1.1 (1.02–1.19)	0	42.9 (41.1–44.9)	0
1 (2244)	Triple line on day before commencing Progesterone	83.77 (81.04–86.25)	18.02 (16.07–20.11)	1.02 (0.98–1.06)	0.9 (0.74–1.09)	41.1 (40.1–42)	38.1 (33.6–42.7)
1 (1512)	Triple line on day of commencing Progesterone	61.65 (58.56–64.66)	44.53 (40.13–49)	1.11 (1.01–1.22)	0.86 (0.76–0.98)	43.1 (40.8–45.5)	37 (34.2–40.1)
1 (236)	Triple line on day of ET	91.96 (85.29–96.26)	11.29 (6.31–18.22)	1.04 (0.95–1.13)	0.71 (0.32–1.58)	41.5 (39.4–43.6)	32.7 (17.9–51.9)
Endometrial volume to predict CP after non-fresh ET							
1 (40)	>3.2 mL on day of ET	80 (28.36–99.49)	77.14 (59.86–89.58)	3.5 (1.65–7.41)	0.26 (0.04–1.51)	70.5 (53–83.5)	15.1 (2.7–50.8)
Endometrial receptivity markers evaluated by endometrial biopsy							
1 (126)	Pinopode score > −26.48	83	45	1.51	0.38	50.8	20.6

LR+ = likelihood ratio of a positive test result; LR− = likelihood ratio of a negative test result.

Nineteen studies provided clinical pregnancy data in relation to endometrial thicknesses cut-offs ranging between 6 and 17 mm as measured on the day of hCG injection for women undergoing IVF with fresh embryo transfer. Sufficient data were available for test accuracy meta-analysis of endometrial thickness cut-offs ranging from 6 to 14 mm.

Overall, the predictive accuracy of endometrial thickness for clinical pregnancy was low, as the hierarchical summary receiver operating characteristic (HSROC) curve for all studies and all endometrial thicknesses cut-offs shows no discrimination between women who achieved a clinical pregnancy and women who did not (area under the HSROC: 0.57 [95% CI: 0.52–0.61], Fig. 4).

The 6 mm cut-off (four studies, 28 868 cycles) had the highest sensitivity (99.6%) and the lowest specificity (0.98%). The 14 mm cut-off (15 studies, 42 163 cycles) had the lowest sensitivity (9.1%) and the highest specificity (92.8%). There was a gradual decrease in sensitivity

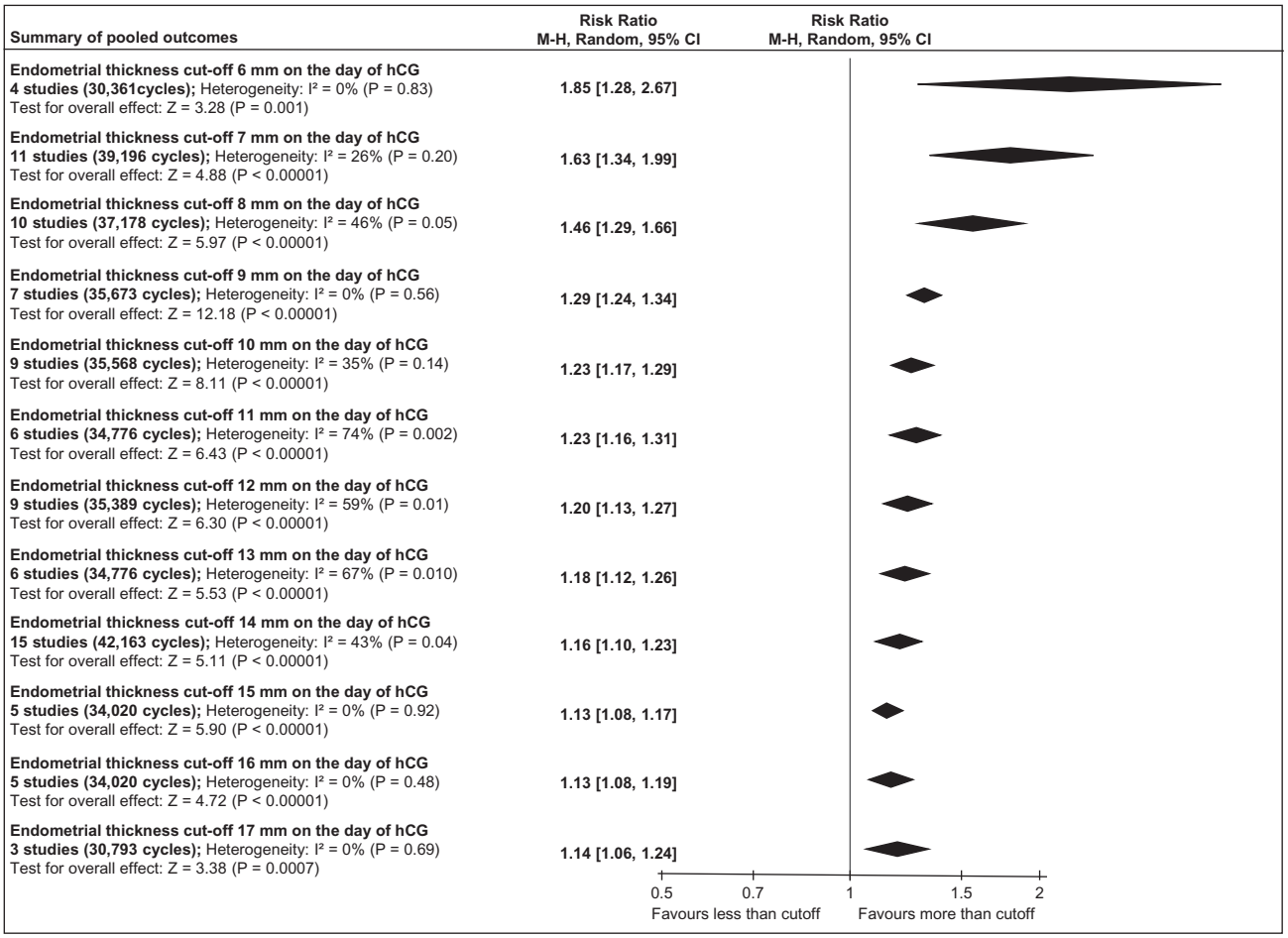

Figure 3 Summary of association between endometrial thickness (ET) cut-offs on the day of hCG injection and clinical pregnancy (CP) for women undergoing IVF with fresh embryo transfer.

and increase in specificity from the 6 mm cut-off to the 14 mm cut-off resulting in area under the receiver operator curve (AUC), ranging between 0.49 and 0.74 (Supplementary Fig. S6).

Insufficient data were available to perform test accuracy meta-analysis based on live birth as an outcome. Live birth accuracy data from the largest study (Gallos *et al.*, 2018) was similar to clinical pregnancy accuracy data.

Endometrial volume

Studies measured the endometrial volume for women undergoing IUI and IVF with fresh or non-fresh embryo transfer. Endometrial volume has been reported on the day of IUI, at various time points in relation to IVF with fresh embryo transfer (day of hCG injection, day of oocyte retrieval, day of embryo transfer), and on the day of non-fresh embryo transfer.

Association analyses (using means): Sufficient data were available to perform meta-analysis of studies reporting the mean endometrial volume between clinical pregnancy and no clinical pregnancy groups in the context of IUI and IVF with fresh and non-fresh embryo transfer.

Four studies reported the endometrial volume for women undergoing IUI. The endometrial volume measured on the day of IUI was higher for women who achieved a clinical pregnancy compared to those who did not (MD, 0.63; 95% CI: 0.03–1.23; $z = 2.05$; $P < 0.04$; four studies; 550 cycles; low heterogeneity: $I^2 = 35\%$, Supplementary Fig. S7).

Eight studies reported endometrial volume for women undergoing IVF with fresh embryo transfer. There was no difference in the endometrial volume measured on the day of hCG injection between women who achieved a clinical pregnancy compared to those who did not (MD, 0.49; 95% CI: −0.23 to 1.2; $z = 1.34$; $P = 0.18$; five studies; 943 cycles; substantial heterogeneity: $I^2 = 69\%$, Supplementary Fig. S8). No difference was also observed between the groups when the endometrial volume was measured on the day of fresh embryo transfer (MD, 0.34; 95% CI: −0.17 to 0.86; $z = 1.31$; $P = 0.19$; three studies; 652 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S8).

Accuracy analyses (using cut-offs): Insufficient data were available to perform meta-analysis of studies reporting various cut-offs for endometrial volume and the corresponding clinical pregnancy rate.

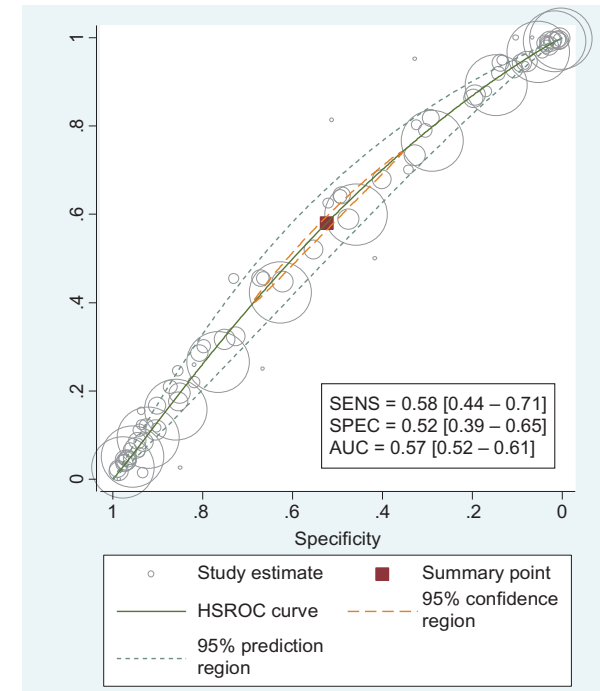

Figure 4 Hierarchical summary receiver operating characteristic curve (HSROC) for endometrial thickness prediction of clinical pregnancy for all cut-off values and all studies reporting on endometrial thickness measurements on the day of hCG injection. Circle size reflects the sample size of the studies. SENS = sensitivity; SPEC = specificity; AUC = area under the curve.

One study (Zollner *et al.*, 2003a) reported clinical pregnancy data following IUI based on the cut-off of 2 mL for endometrial volume as measured on the day of IUI. The sensitivity was 78.6% and the specificity was 56.7% (Table I).

Aboulghar *et al.* (2005) reported clinical pregnancy data following IVF with fresh embryo transfer based on two cut-offs for endometrial volume as measured on the day of hCG injection. The cut-off of 2 mL offered a sensitivity of 93.3% and a specificity of 6.9%, while the cut-off of 4 mL offered a sensitivity of 68.9% and a specificity of 44.8% (Table II).

One study (Zollner *et al.*, 2003b) reported clinical pregnancy data following IVF with fresh embryo transfer based on two cut-offs for endometrial volume as measured on the day of the embryo transfer. The cut-off of 2 mL offered a sensitivity of 93.5% and a specificity of 22.2%, while the cut-off of 2.5 mL offered a sensitivity of 90.3% and a specificity of 35.8% (Table II).

One study (Zollner *et al.*, 2012) reported clinical pregnancy data following IVF with frozen–thawed embryo transfer based on the cut-off of 3.2 mL for endometrial volume as measured on the day of the embryo transfer. The sensitivity was 80% and the specificity was 77.1% (Table III).

Endometrial pattern

Studies assessed the endometrial pattern for women undergoing IUI and IVF with fresh or non-fresh embryo transfer. Endometrial pattern has been reported at various time points in relation to IUI (Day 10 of cycle, day of hCG injection, day of IUI), fresh embryo transfer (luteal phase prior to IVF cycle, day of hCG injection, day after hCG injection, day of oocyte retrieval, day of embryo transfer) and non-fresh embryo transfer (day of donor ovulation, day before commencing progesterone, day of commencing progesterone, day of embryo transfer).

Association analyses: Sufficient data were available to perform meta-analysis of studies reporting the endometrial pattern in the context of IUI and IVF with fresh and non-fresh embryo transfer.

Eight studies reported clinical pregnancy in relation to the endometrial pattern in women undergoing IUI. Triple line pattern assessed on the day of hCG injection was associated with higher clinical pregnancy rates (RR, 1.45; 95% CI: 1.08–1.95; $z = 2.49$; $P < 0.01$; five studies; 1 525 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S9). Triple line pattern assessed on the day of IUI was also associated with higher clinical pregnancy rates (RR, 3.21; 95% CI: 1.35–7.61; $z = 2.64$; $P < 0.008$; three studies; 445 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S9).

Twenty studies reported clinical pregnancy in relation to the endometrial pattern in women undergoing IVF with fresh embryo transfer. There were similar clinical pregnancy rates between women with triple line pattern and women without triple line pattern assessed on the day of hCG injection (RR, 1.05; 95% CI: 0.91–1.22; $z = 0.73$; $P = 0.47$; 11 studies; 15 653 cycles; substantial heterogeneity: $I^2 = 58\%$, Supplementary Fig. S10). Clinical pregnancy rates were also similar between women with triple line pattern and women without triple line pattern assessed on the day after hCG (RR, 2.19; 95% CI: 0.92–5.22; $z = 1.78$; $P = 0.08$; three studies; 719 cycles; substantial heterogeneity: $I^2 = 69\%$, Supplementary Fig. S10). There were also similar clinical pregnancy rates between women with triple line pattern and women without triple line pattern assessed on the day of embryo transfer (RR, 1.02; 95% CI: 0.75–1.4; $z = 0.13$; $P = 0.89$; six studies; 778 cycles; low heterogeneity: $I^2 = 32\%$, Supplementary Fig. S10).

Five studies reported clinical pregnancy in relation to the endometrial pattern for women undergoing IVF with non-fresh embryo transfer. There were similar clinical pregnancy rates between women with triple line pattern and women without triple line pattern assessed on the day of commencing progesterone (RR, 1.78; 95% CI: 0.96–3.29; $z = 1.85$; $P = 0.06$; three studies; 1 870 cycles; substantial heterogeneity: $I^2 = 90\%$, Supplementary Fig. S11).

Accuracy analyses: Sufficient data were available to perform meta-analysis of studies reporting endometrial pattern and the corresponding clinical pregnancy rates for women undergoing IUI and IVF with fresh embryo transfer.

Five studies reported clinical pregnancy data in relation to triple line pattern assessed on the day of hCG injection for women undergoing IUI. The sensitivity was 84.4% and the specificity was 27.2% (five studies, 1525 cycles).

Eleven studies reported clinical pregnancy data in relation to triple line pattern assessed on the day of hCG injection for women undergoing IVF with fresh embryo transfer. The sensitivity was 86.9% and the specificity was 14.8% (11 studies, 15 653 cycles).

Six studies reported clinical pregnancy data in relation to triple line pattern assessed on the day of embryo transfer for women undergoing IVF with fresh embryo transfer. The sensitivity was 69.6% and the specificity was 35.4% (six studies, 778 cycles).

Doppler signals

Studies measured various Doppler indices for women undergoing IUI and IVF with fresh or non-fresh embryo transfer. The measurements were acquired at various time points in relation to IUI (day of hCG injection, day of IUI) and IVF with fresh embryo transfer (day of hCG injection, day of oocyte retrieval, day of embryo transfer), and on the day of non-fresh embryo transfer.

Association analyses (using means): Three studies reported insufficient data to perform meta-analysis of mean Doppler indices between clinical pregnancy and no pregnancy groups in the context of IUI. Riad and Hak (2014) evaluated 90 women undergoing IUI and found lower pulsatility index (PI) and lower resistance index (RI) of the subendometrial blood flow on the day of hCG injection in women who achieved a clinical pregnancy compared to those who did not. Kim *et al.* (2010) evaluated 106 women undergoing IUI and reported higher endometrial vascularity index (VI), flow index (FI) and vascularization flow index (VFI) scores on the day of IUI in women who achieved a clinical pregnancy compared to women who did not. No difference was observed between the groups in subendometrial VI, FI and VFI scores or uterine artery PI, RI, systolic/diastolic (S/D) ratio. Engels *et al.* (2011) evaluated 79 consecutive IUI cycles and reported higher subendometrial FI on the day of hCG injection in women who achieved a clinical pregnancy compared to women who did not become pregnant. No difference was observed in the subendometrial VI or VFI.

Twenty-two studies reported various mean Doppler indices between women who achieved a clinical pregnancy following IVF with fresh embryo transfer and women who did not.

Endometrial VI, measured on the day of hCG injection, was similar between the groups (MD, −0.68; 95% CI: −3.00 to 1.63; $z = 0.58$; $P = 0.56$; four studies; 840 cycles; substantial heterogeneity: $I^2 = 88\%$, Supplementary Fig. S12). When measured on the day of fresh embryo transfer, endometrial VI was higher in women who achieved a clinical pregnancy compared to those who did not (MD, 0.96; 95% CI: 0.06–1.86; $z = 2.08$; $P < 0.04$; two studies; 527 cycles; substantial heterogeneity: $I^2 = 82\%$, Supplementary Fig. S12).

Endometrial FI, measured on the day of hCG injection, was similar between the groups (MD, 0.9; 95% CI: −1.76 to 3.57; $z = 0.67$; $P = 0.51$; three studies; 805 cycles; substantial heterogeneity: $I^2 = 91\%$, Supplementary Fig. S13). Similar results were obtained on the day of the fresh embryo transfer (MD, 2.83; 95% CI: −8.5 to 14.15; $z = 0.49$; $P = 0.62$; two studies; 527 cycles; substantial heterogeneity: $I^2 = 97\%$, Supplementary Fig. S13).

Endometrial VFI, measured on the day of hCG injection, was similar between clinically pregnant and not pregnant women (MD, 1.02; 95% CI: −0.92 to 2.97; $z = 1.02$; $P = 0.3$; three studies; 805 cycles; substantial heterogeneity: $I^2 = 79\%$, Supplementary Fig. S14). Higher endometrial VFI measured on the day of the fresh embryo transfer was observed in women who achieved a clinical pregnancy (MD, 0.21; 95% CI: 0.09–0.33; $z = 3.43$; $P < 0006$; two studies; 527 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S14).

Subendometrial VI, measured on the day of hCG injection, was lower in women who achieved a clinical pregnancy compared to women who did not (MD, −1.71; 95% CI: −3.11 to −0.3; $z = 2.38$; $P < 02$; three studies; 763 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S15). No differences between the groups were observed in subendometrial VI measured on the day of fresh embryo transfer (MD, −0.03; 95% CI: −0.42 to 0.37; $z = 0.13$; $P = 0.9$; two studies; 527 cycles; low heterogeneity: $I^2 = 7\%$, Supplementary Fig. S15).

Subendometrial FI, measured on the day of hCG injection, was higher in women who achieved a clinical pregnancy compared to women who did not (MD, 0.76; 95% CI: 0.22–1.3; $z = 2.74$; $P < 0.006$; two studies; 728 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S16). No differences between the groups were observed in the subendometrial FI measured on the day of fresh embryo transfer (MD, 0.6; 95% CI, −1.77 to 2.97; $z = 0.5$; $P = 0.62$; three studies; 616 cycles; substantial heterogeneity: $I^2 = 75\%$, Supplementary Fig. S16).

Subendometrial VFI, measured on the day of hCG injection was similar between clinically pregnant and not pregnant women (MD, −0.35; 95% CI: −0.81 to 0.12; $z = 1.47$; $P = 0.14$; two studies; 728 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S17). No difference between the groups was observed in the subendometrial VFI measured on the day of the fresh embryo transfer (MD, −0.01; 95% CI: −0.19 to 0.18; $z = 0.05$; $P = 0.96$; two studies; 527 cycles; substantial heterogeneity: $I^2 = 61\%$, Supplementary Fig. S17).

Uterine artery PI, measured on the day of hCG injection, was similar between women who achieved a clinical pregnancy and those who did not (MD, −0.01; 95% CI: −0.14 to 0.12; $z = 0.14$; $P = 0.89$; three studies; 227 cycles; substantial heterogeneity: $I^2 = 59\%$, Supplementary Fig. S18). No difference between the groups was observed in uterine artery PI measured on the day of oocyte retrieval (MD, 0.04; 95% CI: −0.12 to 0.2; $z = 0.49$; $P = 0.62$; two studies; 99 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S18). Similar uterine artery PIs were measured on the day of fresh embryo transfer between clinically pregnant and not pregnant women (MD, −0.07; 95% CI, −0.19 to 0.12; $z = 1.1$; $P = 0.27$; seven studies; 1 487 cycles; substantial heterogeneity: $I^2 = 72\%$, Supplementary Fig. S18).

Uterine artery RI, measured on the day of fresh embryo transfer, was similar between clinically pregnant and not pregnant women (MD, −0.01; 95% CI: −0.03 to 0; $z = 1.72$; $P = 0.09$; four studies; 1318 cycles; substantial heterogeneity: $I^2 = 67\%$, Supplementary Fig. S19).

Three studies reported mean Doppler indices in relation to clinical pregnancy following IVF with frozen–thawed embryo transfer. Data were insufficient for meta-analysis. One study (Son *et al.*, 2014) assessed 70 women on the day of embryo transfer and reported similar uterine artery PIs and RIs and subendometrial RIs and PIs between clinically pregnant and not pregnant women. One study (Nandi *et al.*, 2014) assessed 45 women at various times in relation to the embryo transfer and found no differences in endometrial VI, FI and VFI between women who achieved a clinical pregnancy and those who did not. One study (Polanski *et al.*, 2016) correlated manual and spherical endometrial spatio-temporal image correlation (STIC) vascularity indices for 127 women undergoing fresh and frozen–thawed embryo transfers to report no difference between clinically pregnant and not pregnant women.

Association analyses (using cut-offs): Sufficient data were available for meta-analyses in the context of IVF with fresh embryo transfer.

The presence of endometrial blood flow on the day of hCG injection was associated with higher clinical pregnancy rates (RR, 1.98; 95% CI: 1.37–2.86; $z = 3.63$; $P < 0.0003$; three studies; 393 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S20). The presence of endometrial blood flow on the day of fresh embryo transfer was not associated with clinical pregnancy (RR, 1.82; 95% CI: 0.98–3.37; $z = 1.91$; $P = 0.06$; three studies; 945 cycles; substantial heterogeneity: $I^2 = 79\%$, Supplementary Fig. S20).

A uterine artery PI of <3 measured on the day of fresh embryo transfer was associated with higher clinical pregnancy rates (RR, 3.07; 95% CI,: 1.54–6.12; $z = 3.18$; $P < 0.001$; three studies; 400 cycles; no heterogeneity: $I^2 = 0\%$, Supplementary Fig. S21).

Accuracy analyses: Insufficient data were available to perform accuracy meta-analysis of studies reporting Doppler indices and the corresponding clinical pregnancy rates. Accuracy measurements from the largest study reporting each Doppler index and cut-off value are presented in Tables I–III.

Endometrial wave-like activity

Six studies assessed the relation between endometrial wave-like activity and pregnancy outcomes in natural cycles, IUI and IVF with fresh and frozen–thawed embryo transfer. Data were insufficient for meta-analysis.

IJland *et al.* (1997) recruited 33 couples with unexplained infertility and assessed the endometrial activity throughout the menstrual cycle using ultrasound recordings for 3–15 min. Women who conceived (9/33, 27%) during the study cycle had lower endometrial wave-like activity compared to women who conceived in later cycles or those who never conceived.

Kim *et al.* (2014) evaluated the endometrial activity for 3 min on the day of IUI for 241 cycles. Women who achieved a clinical pregnancy (49/241, 20.3%) displayed reduced endometrial activity overall, but had a higher cervico-fundal movement rate.

Swierkowski-Blanchard *et al.* (2017) recorded 5 min of uterine activity for 100 women undergoing IUI. Women with clinical pregnancy following IUI (18/100, 18%) were more likely to have low frequency and high intensity uterine contractions compared to women who failed to conceive.

Chung *et al.* (2017) evaluated the changing pattern of uterine contractions in 286 women undergoing IVF with fresh embryo transfer. Ultrasound recordings were acquired 5 min before, 5 min after and 60 min after the embryo transfer. There was no difference in uterine contractility 5 min before the embryo transfer between the clinically pregnant and not pregnant groups; however, the contraction frequency measured 5 min after the embryo transfer was reduced in women who achieved a clinical pregnancy.

Fanchin *et al.* (1998) monitored the uterine activity for 5 min just before fresh embryo transfer in 220 cycles. A stepwise decrease in clinical and ongoing pregnancy rates occurred from fewer than 3 contractions/min to more than 5 contractions/min.

Zhu *et al.* (2014) evaluated the uterine peristaltic wave frequency before 292 fresh and frozen–thawed embryo transfers. The clinical pregnancy rate was the highest when fewer than 2 waves/min were observed, and it decreased significantly for women with more than 3 waves/min.

Endometrial receptivity markers evaluated by endometrial biopsy

Histology and cytology

Studies correlated histological appearances and cytological compartments of the endometrium in the context of natural conception and IVF. Data were insufficient for meta-analysis.

Three studies used Noyes *et al.*'s (1950) histological criteria for endometrial dating in women with unexplained infertility. The endometrial biopsies were performed in the mid-luteal phase of an ovulatory cycle.

Driessen *et al.* (1980) divided 232 infertile women into four groups based on endometrial dating: 'no delay of the secretory phase, a secretory phase with a delay of 2 days, a secretory delay of 3 days or more, and an endometrium which could not be dated because of inadequate material'. No differences were reported in pregnancy rates within two years between the four groups.

Balasch *et al.* (1992) evaluated 1492 endometrial biopsies taken from 1055 women diagnosed with unexplained infertility. Authors reported no association between histological endometrial adequacy in the cycle of conception or in previous cycles and the outcome of pregnancy.

Klentzeris *et al.* (1992) divided 47 women based on endometrial dating into 'in phase' or 'retarded' endometrium and assessed their pregnancy outcomes in the following 3 years. Women with 'in phase' endometrium were more likely to become pregnant (18/36, 50%) following IVF compared to women with 'retarded' endometrium (1/11, 9%).

Three studies evaluated the association between uterine natural killer (uNK) cells and the outcome of subsequent pregnancies in women who suffered unexplained recurrent miscarriage. The endometrial biopsies were timed in the window of implantation dated in relation to the LH surge or confirmed by histological criteria.

Tuckerman *et al.* (2007) assessed the percentage of stromal cells positive for CD56 in women with three or more unexplained recurrent miscarriages ($n = 87$). Similar $CD56^+$ cell counts were observed in 19 women who miscarried (mean 9.6%, range: 1.7–25.0%) and 32 women who had a live birth (mean 13.3%, range: 1.1–41.4%) in the subsequent pregnancy.

Quenby *et al.* (1999) assessed various endometrial leucocytes in 22 women with three or more unexplained recurrent miscarriages, out of which 15 obtained a subsequent pregnancy completed by miscarriage or live birth. Higher percentages of $CD4^+$, $CD8^+$, $CD14^+$, $CD16^+$ and $CD56^+$ cells were observed in women who miscarried (4/15) compared to women who achieved a live birth (11/15) in the subsequent pregnancy. There were no differences of $CD45^+$, $CD3^+$, $CD22^+$, $CD57^+$ or $CD69^+$ between the groups.

Michimata *et al.* (2002) assessed various endometrial leucocyte subsets in 17 women who suffered two or more recurrent miscarriages. No difference in $CD45^+$, $CD56^+$, $CD16^+$, $CD20^+$, $CD3^+$ or $CD8^+$ cells were observed between women who achieved a live birth (11/17, 65%) and women who miscarried (6/17, 35%) in the subsequent pregnancy.

Liu *et al.* (2014) combined the histological criteria with uNK count to predict the fate of future pregnancies in 83 women diagnosed with recurrent miscarriage or recurrent implantation failure. No correlation

was observed between uNK count and subsequent pregnancy outcome. 'Retarded' endometrium was associated with a higher miscarriage rate (13/19, 68%) compared to 'in phase' endometrium (23/64, 35%). Combining uNK count and histological dating increased their individual prognostic value.

Two studies correlated pinopode formation with subsequent pregnancy outcomes. Pantos *et al.* (2004) assessed the pinopode formation in a mock cycle for 46 women scheduled to undergo IVF with donated oocytes. The embryo transfer was then timed in relation to previous cycle's pinopode formation. Higher clinical pregnancy (76.47 versus 33.33%) and live birth (67.64 versus 25%) rates were observed in women with delayed embryo transfer as directed by pinopode formation compared to women with standard embryo transfer.

Jin *et al.* (2017) reported a custom scoring system for the pinopode formation in 126 women undergoing frozen–thawed embryo transfer. Pinopode index scores higher than −26.48 were associated with higher clinical pregnancy rates compared to lower scores. This pinopode index score cut-off had 83% sensitivity and 45% specificity for clinical pregnancy (Table III).

Endometrial receptivity array

Endometrial receptivity array (ERA) is a molecular diagnostic test based on microarray technology that classifies endometrial biopsies into receptive, prereceptive or proliferative based on the expression of 238 selected genes (Díaz-Gimeno *et al.*, 2011). Women then undergo personalized embryo transfer (pET) where the frozen–thawed embryo transfer is timed according to the receptive status as identified by ERA. Five studies reported clinical outcomes following the use of ERA and pET in women with previous unsuccessful embryo transfers. Meta-analysis was not performed due to clinical and methodological heterogeneity in patient populations (number of previously failed cycles), reported comparisons and unit of analysis (per couple or per cycle).

One study (Ruiz-Alonso *et al.*, 2013) assessed the endometrial receptivity in 85 women scheduled to undergo frozen–thawed embryo transfer in natural or hormonally prepared cycles. ERA test identified a higher rate of non-receptive endometrium in women with recurrent implantation failure (22/85, 25.9%) compared to women without recurrent implantation failure (3/25, 12%). Women diagnosed with non-receptive endometrium on the initial ERA test achieved a pregnancy rate of 50% (four out eight women with follow-up data) after pET.

One study (Ruiz-Alonso *et al.*, 2014) reported on 17 women who failed to achieve ongoing pregnancies following standard embryo transfer on a day in which the endometrium was diagnosed as non-receptive (pre- or post-receptive) by the ERA test. The same 17 women underwent a total of 20 subsequent pET based on ERA result and 53% (9/17) reached the stage of ongoing pregnancy.

Mahajan (2015) reported a higher rate of non-receptive endometrium in women who suffered two or more implantation failures (22/80, 28%) compared to women who suffered only one implantation failure (14/93, 15%) following IVF with standard embryo transfer of good quality embryos. The use of pET led to similar ongoing pregnancy rates between women diagnosed with non-receptive endometrium (20/48, 42%) compared to women diagnosed with receptive endometrium (8/18, 44.5%) on the initial ERA test.

Hashimoto *et al.* (2017) performed ERA testing on 50 women with recurrent implantation failure and reported non-receptive endometrium at a rate of 24% (12/50). The clinical pregnancy rate in the subsequent pET was higher in women with non-receptive endometrium based on the ERA test (5/10, 50%) compared to women with standard embryo transfer (12/34, 35.3%).

Tan *et al.* (2018) assessed endometrial receptivity in 88 women and reported an overall non-receptive rate of 44.3% (39/88). The rate of non-receptive endometrium was 37.5% (18/48) in women with at least one failed frozen–thawed euploid embryo transfer. Ongoing pregnancy rates following the subsequent embryo transfer were similar between women who had a receptive endometrium (50.9%) and those who were non-receptive and required pET (51.6%).

Díaz-Gimeno *et al.* (2017) analysed 771 women diagnosed by ERA and further stratified the receptive endometrium based on the outcome following pET (biochemical pregnancy vs live birth) to identity additional transcriptomic profiles: proliferative, early prereceptive, late prereceptive, receptive, late receptive and post-receptive. The ongoing pregnancy rates ranged between 76.9 and 80% in the late prereceptive and receptive signatures compared to 33.3% in the late receptive endometrium.

Other molecular markers

Various individual molecular markers have been investigated by studies with sample sizes ranging from 20 to 122. Data were insufficient for meta-analyses and none of the markers were further developed as diagnostic tests.

Five studies (Thomas *et al.*, 2003; Brosens *et al.*, 2004; Wang *et al.*, 2008; Almquist *et al.*, 2017; Silveira *et al.*, 2017) reported clinical pregnancy in relation to expression levels of BLC6, aromatase P450, α-inhibin and β-glycan, integrins and L-selectin ligand, respectively. Accuracy measures in relation to reported cut-offs were presented in and Table II.

Ten studies (Rizk *et al.*, 1992; Damario *et al.*, 2001; Jinno *et al.*, 2001; Shamonki *et al.*, 2006; Foulk *et al.*, 2007; Serafini *et al.*, 2008, 2009; Seo *et al.*, 2011; Maia-Filho *et al.*, 2015; Krylova *et al.*, 2016) compared subsequently pregnant versus not pregnant women based on mean measurements of various integrins, L-selectin ligand, VEGF, matrix metalloproteinases and E-cadherin expression, alpha-2 PEG, hCG-LH receptor, LIF, macrophage colony-stimulating factor, HOXA-10 and vascular endothelial growth factor A. No convincing evidence for clinical use emerged from these studies.

Endometrial receptivity markers evaluated by endometrial fluid aspirate

Studies correlated endometrial receptivity markers from endometrial fluid aspirate with pregnancy outcomes following IUI or IVF. Data were insufficient for meta-analysis and none of the markers were further developed into diagnostic tests.

Four studies (Halperin *et al.*, 1995; Lédée-Bataille *et al.*, 2004; Florio *et al.*, 2008, 2010) provided clinical pregnancy data based on cut-offs for urocortin, activin A, human decidua-associated protein (hDP) and interleukin-18. Their accuracy measures are presented in Tables I and II.

Six studies (Lédée-Bataille et al., 2002; Gillott et al., 2008; Boomsma et al., 2009a,b; Bentin-Ley et al., 2011; Rahiminejad et al., 2015, 2016) evaluated the mean levels of various cytokines, glycodelin, isoforms of leucine-rich alpha2-glycoprotein, LIF and TNF, interleukin-1β, TNF-α, interferon gamma-induced protein 10 and monocyte chemoattractant protein between various outcome groups following fertility treatments. No convincing evidence for clinical use emerged from these studies.

Endometrial receptivity markers evaluated by hysteroscopy

The mid-luteal endometrium was classified as 'good' based on the ring type aspect of the glandular openings and presence of well-developed varicose-like vessels during hysteroscopic assessment (Inafuku, 1992). Four studies reported pregnancy outcomes following the assessment of endometrial receptivity by hysteroscopy in the mid-luteal phase of a natural cycle. Data were insufficient for meta-analysis.

Li et al. (2010) evaluated 79 ovulatory infertile women and reported 'poor' mid-luteal endometrium at a rate of 67.1% (53/79). The clinical pregnancy rate following fertility treatment (ovulation induction, IUI or IVF) was higher in women with 'good' endometrium (14/26, 53.9%) compared to women with 'poor' endometrium (14/53, 26.4%).

Masamoto et al. (2000) evaluated 160 ovulatory infertile women and reported 'poor' midsecretory endometrium at a rate of 61.3% (98/160). The miscarriage rate was higher in women with 'poor' endometrium (33/98, 33.7%) compared to women with 'good' endometrium (9/62, 14.5%).

Sakumoto et al. (1992) investigated 61 women prior to IVF and reported 'poor' mid-luteal endometrium at a rate of 50.8% (31/61). The pregnancy rate after IVF was higher in women with 'good' endometrium (12/30, 40%) compared to women with 'poor' endometrium (4/31, 13%).

Santi et al. (2012) assessed the endometrium of 162 infertile women and reported a 33% (54/162) rate of 'poor' endometrium. The pregnancy rate after fertility treatments was higher in women with 'good' endometrium (47/108, 43.5%) compared to women with 'poor' endometrium (13/54, 24%).

Jinno et al. (2001) used the hysteroscopic approach to measure the endometrial blood flow between luteal days 4 and 6 in 75 women scheduled to undergo IVF. The cut-off endometrial blood flow of 29 mL/min/100 g of tissue had a sensitivity of 71.4% and a specificity of 61.1% for clinical pregnancy (Table II).

Discussion

Successful implantation involves complex interactions between the embryo and the endometrium. Receptivity and selectivity are two intrinsic functions of the endometrium that facilitate the recognition of a high quality embryo and nurture its development into a normal foetus. Embryos with reduced potential to develop into a normal foetus are declined implantation, allowing the woman to preserve her resources for the next menstrual cycles. Embryos account for one-third of implantation failures, while suboptimal endometrial receptivity and altered embryo–endometrial dialogue are responsible for the remaining two-thirds (Fig. 5).

The present review identified a large variety of endometrial receptivity markers correlated with clinical outcome data in the context of natural conception, IUI and IVF with fresh or non-fresh embryo transfer. The markers were evaluated by ultrasound, endometrial biopsy, endometrial fluid aspirate and hysteroscopy. The overall quality of the studies was moderate due to low scores obtained for cohort comparability as confounding factors were very rarely accounted for. Associations were identified between clinical pregnancy and various endometrial receptivity markers (endometrial thickness, endometrial pattern, Doppler indices, endometrial wave-like activity and various molecules); however, their poor ability to predict clinical pregnancy (Tables I–III) prevents them from being used as diagnostic tests of endometrial receptivity.

Endometrial thickness was the most commonly investigated marker of endometrial receptivity. The pooled data from association studies revealed no clinically significant difference in endometrial thickness between pregnant and non-pregnant women following IUI and IVF. In addition, high quality evidence from accuracy studies pooled in our meta-analysis revealed a poor ability to predict clinical pregnancy. Two recent meta-analyses of endometrial thickness during IUI reported no evidence for an association (Weiss et al., 2017) or uncertain association based on the mean endometrial thickness (Gadalla et al., 2018). The sROC curve calculated in a previous meta-analysis shows that endometrial thickness does not discriminate between cases that achieved a clinical pregnancy following IVF and cases that did not (Kasius et al., 2014).

Other markers of endometrial receptivity measured by ultrasound (endometrial volume, endometrial pattern, Doppler signals, wave-like activity) were supported by low to very low quality of evidence, due to bias (no adjustment for important prognostic factors), inconsistency (significant heterogeneity) and imprecision (caused by the small number of participants and events). A recent meta-analysis reported

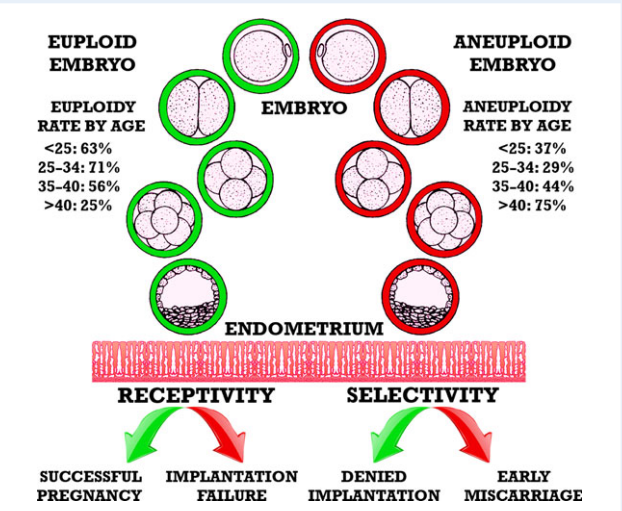

Figure 5 The fate of pregnancy depending on the quality of the embryo and the intrinsic functions of the endometrium (receptivity and selectivity).

statistically significant associations between various Doppler signals and pregnancy rates; however, their clinical relevance remains uncertain and further studies were advised (Wang *et al.*, 2018).

The major limiting factor for the quality of the evidence supporting markers of endometrial receptivity measured by endometrial biopsy, endometrial fluid aspirate or hysteroscopy was imprecision. Most of the markers were investigated by small single studies leading to uncertainty regarding reproducibility, true effect and clinical value.

The groundwork in transcriptomic characterization of the endometrial cycle (Ponnampalam *et al.*, 2004; Talbi *et al.*, 2006) culminated with the development of the ERA diagnostic test for endometrial receptivity. Studies reported promising results following the use of ERA testing coupled with pET as an intervention to address non-receptive endometrium; however, insufficient data were available to compare the outcomes following embryo transfer in receptive versus non-receptive endometrium as assessed by ERA. Additional information about its clinical value will become available with the publication of the ongoing randomized controlled trial (ClinicalTrials.gov Identifier: NCT01954758). ER Map/ER Grade is a new endometrial receptivity test based on the expression of 184 genes involved in endometrial proliferation and maternal immune response associated to embryonic implantation (Enciso *et al.*, 2018). Studies have not yet evaluated its clinical value.

Means are not useful for endometrial receptivity

Endometrial thickness was the most investigated marker of endometrial receptivity and has become a classic example to demonstrate limited benefit of means in the context of endometrial receptivity. The mean endometrial thickness difference between women who achieved a clinical pregnancy and women who did not ranged from only −0.5 to 1.16 mm at various times during IUI and IVF with fresh or non-fresh embryo transfers. Despite this small difference being statistically significant on few occasions, it is unlikely to be considered a clinically significant difference given the inter-observer variation of 1.5 mm (Karlsson *et al.*, 1994).

Given the similar mean endometrial thicknesses in the clinically pregnant and not pregnant women, one may assume that endometrial thickness is not associated with clinical pregnancy and not an useful test. However, association analyses based on cut-off measures identified significant associations between thicker endometrium and higher pregnancy rates for every cut-off. Furthermore, there may be a biological gradient with the strongest association identified for the 6 mm cut-off (RR 1.85, 95% CI: 1.28–2.67 in favour of thicker than 6 mm endometrium).

Impaired endometrial receptivity may be characterized by extreme values of a continuous endometrial receptivity marker which may have a low incidence (e.g. the incidence of thinner than 6 mm endometrium on the day of hCG injection was 0.33%). Means, which report the average across the whole cohort population, may fail to account for important findings at the extreme levels of the range of observations.

Limitations

In the absence of a gold standard diagnostic test for endometrial receptivity, we considered clinical pregnancy as a proxy outcome to confirm receptive endometrium. However the absence of a clinical pregnancy may be a consequence of embryo quality (aneuploidy or poor implantation potential) or other factors (for example, abnormal endometrial microbiome, structural uterine defects or systemic maternal conditions) and may not necessarily reflect the absence of endometrial receptivity. This may underestimate the accuracy of the biomarkers we reviewed.

Insufficient data were available to explore the sources of substantial heterogeneity between the studies pooled in the meta-analyses. Various ultrasound scanning machines, measurement techniques, classification systems and tissue/sample processing protocols were used by individual researchers. Studies included diverse populations and lacked adequate details related to known sources of heterogeneity (infertility duration, stage of embryo at transfer, embryo quality, number of transferred embryos or number of previous failed cycles).

It was not feasible to contact authors for further clarifications due to the large number of included studies published over several decades. Only studies published in full manuscript were included, while studies published as abstracts might have reported on additional markers of endometrial receptivity.

Strengths

This is the first systematic review to summarize the clinical value of existing endometrial receptivity markers. We have performed both association and accuracy analyses to enable comparisons between various endometrial receptivity markers.

We have conducted a very broad literature search to give an accurate overview of the current progress in the diagnosis of endometrial receptivity. This allowed the inclusion of 163 studies reporting on more than 40 markers of endometrial receptivity correlated with subsequent pregnancy outcomes.

Various endometrial receptivity markers were analysed and reported according to the context (natural conception, IUI, IVF with fresh or non-fresh embryo transfer) and timing of measurement (before the start of treatment cycle, at various times during ovarian stimulation or on the day of oocyte retrieval, IUI or embryo transfer, etc.) to account for some potential sources of heterogeneity.

Implications for clinical practice

None of the endometrial receptivity markers included in the present review has sufficient discriminatory value to act as a diagnostic test for endometrial receptivity based on their ability to predict clinical pregnancy. The post-test probabilities presented in Tables I–III may be used in clinical practice to manage couples' expectations during fertility treatments. Further data relevant to the clinical value of the modern molecular tests of endometrial receptivity (ERA, ER Map/ER Grade) are awaited.

Implications for further research

The time has come to reconsider the classical definition for the window of implantation as a time frame of maximal endometrial receptivity surrounded by refractory endometrium. Endometrial receptivity appears to be a continuous variable reflected in the molecular changes triggered by ovulation and progesterone exposure.Various levels of endometrial receptivity exist within the window of

implantation as identified by different transcriptomic signatures coupled with different pregnancy outcomes (Díaz-Gimeno et al., 2017). The transition from non-receptive endometrium to increasing levels of endometrial receptivity that reach a maximal receptivity followed by decreasing levels of endometrial receptivity has also been suggested by the poor pregnancy outcomes associated with late implantation (Wilcox et al., 1999; Jukic et al., 2011; Asvold et al., 2014).

Quantifying endometrial receptivity by endometrial biopsy postpones the completion of fertility treatment due to the invasiveness of the procedure. Endometrial fluid aspirate is less invasive and may be performed before embryo transfer without affecting the pregnancy outcome in a negative way (van der Gaast et al., 2003; Boomsma et al., 2009a,b). Furthermore, endometrial fluid aspirate analysis correlates with endometrial biopsy results (Vilella et al., 2017).

Single molecule testing may not be sufficient to describe the complexity of endometrial receptivity and transcriptomic profiles may be more reliable (Zhang et al., 2013). The dynamic, cyclic nature of the endometrium suggests that it may be difficult, if not impossible, to reliably assess endometrial function on the basis of a single test (i.e. a snapshot) given, for example, how dynamic the uNK cells are from one cycle to the next (Brighton et al., 2017). Next-generation sequencing and various omics- techniques offer an unprecedented opportunity to investigate novel endometrial receptivity markers.

Further research of continuous endometrial receptivity markers should avoid comparing study groups by means alone and should aim to identify cut-off levels that provide maximum accuracy measures. Cumulative pregnancy rates may be a more robust way to evaluate the efficacy of an endometrial test, considering the high incidence of failures that may either be iatrogenic or embryonic in origins.

Increasing value and reducing waste in endometrial receptivity research

Chalmers and Glasziou (2009) estimated that 85% of research funding was being avoidably wasted across the clinical, health services and basic science research. Their article was followed by the publication of the 'Research: increasing value, reducing waste' series in The Lancet. The series included five articles describing ways to increase the value and reduce the waste at various levels in biomedical research: priorities setting, design and conduct, regulation and management, accessibility and reporting. Future studies in the field of endometrial receptivity may benefit directly from recommendations related to design and conduct (Ioannidis et al., 2014) and reporting (Glasziou et al., 2014).

In terms of study design and conduct, a detailed protocol published prior to starting a study will improve the overall poor documentation of endometrial research. Reproducibility of research suffers from the lack of details in study design, starting with population selection, continuing with the measurement of the proposed endometrial receptivity marker, and ending with reporting of results. Most novel endometrial receptivity markers will not allow accurate power or sample size calculations; however, some rational design calculations should be done at least for foreseeable variables at the time of study design (i.e. anticipated overall clinical pregnancy rate). Prospective longitudinal cohort studies may be most appropriate for investigating prognostic markers of endometrial receptivity, while the multicentre approach may address some of the biases induced by small, single-centre studies.

The final report of the study should be based on the pre-published protocol. Deviations from the protocol do not automatically lessen the quality of the study as long as they are accounted for and explained. Several reporting standards exist to facilitate the transparency of reports (STROBE (Vandenbroucke et al., 2007) for observational studies, STARD (Cohen et al., 2016) for diagnostic studies). Future study publications should consider reporting on measures that allow comparison to previously published research in order to integrate the new findings in the overall context.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

L.C. designed the study, ran the literature search, extracted data, performed the association analyses and drafted the article. I.G. contributed to the literature search, checked extracted data, performed accuracy analyses and critically revised the article. J.C., T.B., S.Q. and J.J.B. interpreted the data and critically revised the article. A.C. contributed to the study design, interpreted the data and critically revised the article. All authors approve the final version of the article.

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Conflicts of interest

None of the authors have any conflict of interest related to this publication.

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