Human Reproduction, Vol.32, No.5 pp. 1009–1018, 2017
Advanced Access publication on February 23, 2017 doi:10.1093/humrep/dex035

human reproduction

REVIEW *Infertility*

Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis

N.S. Weiss[1,2], M.N. van Vliet[1], J. Limpens[3], P.G.A. Hompes[2], C.B. Lambalk[2], M.H. Mochtar[1], F. van der Veen[1], B.W.J. Mol[4], and M. van Wely[1,*]

[1]Center for Reproductive Medicine, Academic Medical Center, 1105 AZ Amsterdam, The Netherlands [2]Center for Reproductive Medicine, VU Medical Center, Amsterdam, The Netherlands [3]Medical Library, Academic Medical Center, Amsterdam, The Netherlands [4]The Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, Australia

*Correspondence address. Center for Reproductive Medicine, Department of obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands. E-mail: m.vanwely@amc.uva.nl

Submitted on October 5, 2016; resubmitted on December 9, 2016; accepted on January 16, 2017

STUDY QUESTION: Is pre-ovulatory endometrial thickness (EMT) in women with unexplained subfertility undergoing IUI with ovarian stimulation (OS) associated with pregnancy chances?

SUMMARY ANSWER: We found no evidence for an association between EMT and pregnancy chances.

WHAT IS KNOWN ALREADY: It has been suggested that OS with clomiphene citrate (CC) results in a lower EMT than with gonadotrophins or aromatase inhibitors, but the clinical consequences in terms of pregnancy are unclear.

STUDY DESIGN, SIZE, DURATION: We performed a systematic review and meta-analysis of studies comparing CC, gonadotrophins or aromatase inhibitors in an IUI program reporting on EMT and pregnancy rates in women with unexplained subfertility.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We searched MEDLINE, EMBASE and the non-MEDLINE subset of PubMed from inception to 28th June 2016 and cross-checked references of relevant articles. Outcome measures were clinical pregnancy rate and mean pre-ovulatory EMT. We calculated mean differences (MD) with 95% CIs with a fixed effect model, and in case of heterogeneity with an $I^2 > 50\%$ a random effect model. We performed a meta-regression analysis to determine if stimulating drugs interacted with the estimated effect of EMT.

MAIN RESULTS AND THE ROLE OF CHANCE: Our search retrieved 1563 articles of which 23 were included, totaling 3846 women. There were 17 RCTs and 6 cohort studies. The average study quality was low and there was considerable to substantial statistical heterogeneity. Seven studies provided data on EMT in relation to pregnancy. There was no evidence of a difference in EMT between women who conceived and women that did not conceive (1525 women, MD_{random}: 0.51 mm, 95% CI: −0.05 to 1.07). Women treated with CC had a significantly thinner EMT than women treated with gonadotrophins (two studies, MD: −0.33, 95% CI: −0.64 to −0.01). There was no evidence of a difference in EMT when comparing CC with letrozole (five studies, MD_{random}: −0.84, 95% CI: −1.97 to 0.28). The combination of CC plus gonadotrophins resulted in a slightly thinner endometrium than letrozole (nine studies, MD_{random}: −0.79, 95% CI: −1.37 to −0.20). Letrozole resulted in a thinner EMT than gonadotrophins (two studies, MD_{random}: −1.31, 95% CI: −2.08 to −0.53).

LIMITATIONS, REASONS FOR CAUTION: The overall quality of the included studies was low to moderate. We found considerable to substantial heterogeneity in the comparisons, hampering firm conclusions.

WIDER IMPLICATIONS OF THE FINDINGS: We found no evidence for an association between EMT and pregnancy rates during IUI–OS. As a consequence, canceling IUI cycles because of a thin endometrial lining may negatively affect clinical care. Although we found some

evidence for very small differences in EMT when comparing various drugs, we cannot make inferences on their effect on pregnancy chances since these differences may be coincidental.

STUDY FUNDING/COMPETING INTEREST(S): None.

REGISTRATION NUMBER: N/A.

Key words: ovarian stimulation / IUI / endometrium / endometrial thickness / pregnancy rates

Introduction

IUI with ovarian stimulation (IUI–OS) is perceived as a simple, non-invasive and non-expensive first-line treatment for women diagnosed with unexplained or mild male subfertility (Ombelet *et al.*, 2008). The most frequently used drugs for OS are anti-estrogens, such as clomiphene citrate (CC), aromatase inhibitors, such as letrozole and anastrozole, or gonodotrophins, such as HMG purified urinary FSH (uFSH) or recombinant FSH (rFSH). These drugs not only stimulate the growth of multiple follicles, but also proliferate the endometrium. The effect of this proliferation on the chances of conception is unclear.

Data on endometrial thickness (EMT) and pregnancy rates are scarce and conflicting. In some small retrospective cohort studies evaluating EMT in women undergoing IUI–OS with CC ($N = 81$), HMG ($N = 24$ and $N = 112$) or both ($N = 81$) a thin endometrium was associated with lower chances of conception and when the endometrium measured <6 to <8 mm conceptions did not occur at all (Dickey *et al.*, 1993a; Isaacs *et al.*, 1996; Reuter *et al.*, 1996; Warrington *et al.*, 2008). In one of the studies in which HMG was given ($N = 112$), 35 of the total of 38 pregnancies (91%) originated in cycles with an EMT of ≥10 mm (Isaacs *et al.*, 1996). Similarly, a prospective study analyzing 270 women undergoing IUI–OS with CC, HMG and the combination of both found no pregnancies when the endometrium was below 6 mm (Dickey *et al.*, 1993b). In contrast, a prospective cohort study of 593 IUI–OS cycles with gonadotrophins found no correlation between EMT and cumulative pregnancy rate after three treatment cycles (De Geyter *et al.*, 2000). Another prospective study evaluating 168 women treated with CC observed no difference in EMT in women who did or did not conceive (Kolibianakis *et al.*, 2004).

In some studies OS with CC resulted in a thinner EMT than in natural cycles (Nakamura *et al.*, 1997; Dehbashi *et al.*, 2003; Haritha and Rajagopalan, 2003) or than in cycles stimulated with HMG (Gonen and Casper, 1990). A review that evaluated EMT values in letrozole and CC cycles in women with unexplained subfertility found no evidence of a difference in EMT (Liu *et al.*, 2014). This review did not include comparisons with other stimulating drugs, for example gonadotrophins.

Since the association between EMT and pregnancy rates and the interaction between type of drug and EMT in women undergoing IUI–OS has not been assessed systematically, the aims of the present systematic review and meta-analysis were to assess first whether EMT is associated with pregnancy rates and second whether the type of drug affects EMT in women undergoing IUI–OS.

Materials and Methods

Our review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines for reporting. A medical librarian (J.L.) performed a comprehensive literature search in OVID MEDLINE, OVID EMBASE and the non-MEDLINE subset of PubMed from inception to 28th June 2016, to identify publications on EMT and pregnancy rates after IUI–OS. The search strategy, using both text words and MESH/Emtree terms, consisted of two parts. The first was a search for EMT combined with terms for IUI, ART, CC, subfertility or spontaneous pregnancy.

The second was a search for prognostic studies on pregnancy success using IUI alone or IUI–OS. This enables the retrieval of papers that mention EMT in the full text but not in the title or abstract.

The MEDLINE search is shown in Supplementary Table S1. We used no language or other restrictions. The search included an iterative process to refine the search strategy through adding search terms to identify new relevant citations, i.e. via reference and citation checking of relevant trials in Web of Science. We imported and de-duplicated the retrieved bibliographic records using EndNote® X7.5 software (Thomson Reuters, New York, NY, USA).

Two reviewers (M.v.V. and N.W.) independently screened titles and abstracts of the identified studies and read the full articles for final inclusion. The reviewers checked cross references of the detected articles. The reviewers extracted the data from the included articles by using standardized data extraction forms. To assess study quality we used the risk of bias in non-randomized (Sterne *et al.*, 2016) assessment tool checklist for observational studies and the risk of bias assessment tool for RCTs (Cochrane Handbook) (Table I). We then extracted study data and if data were missing, we contacted authors by email. Disagreement between the reviewers was resolved through discussion with a third reviewer (M.v.W.). Risk of bias per study was expressed in the forest plots as colored dots, with red dots meaning high risk of bias, yellow unclear risk of bias and green low risk of bias. Pooled evidence was scored using Grade Profiler 3.6.1 as very low, low, moderate or high.

We included RCTs and cohort studies evaluating pregnancy rates after IUI–OS in women with unexplained infertility or mild male infertility. In case of randomized cross-over trials, we only used pre-cross-over data.

Table I Risk of bias scoring* for RCTs and cohort studies.

	RCT (Cochrane risk of bias)	Cohort (ROBINS-I) bias due to …
A	Random sequence generation	Confounding
B	Allocation concealment	Selection of participants
C	Blinding	Classification of intervention
D	Detection bias	Deviations from intervention
E	Incomplete outcome data	Missing data
F	Selective reporting	Measurement of outcome
G	Other bias	Selection of reported results

*The different scoring items A until G are reflected in Figs 2–5 as red, yellow or green dots.

Studies had to compare CC, aromatase inhibitors (letrozole and anastrozole), gonadotrophins or any combination of these drugs with each other or with any combination thereof and to report on pre-ovulatory EMT and/or EMT in pregnant and non-pregnant women. There was no limit for female age. The articles had to be written in English with full text available. We excluded trials in which estrogen was added to OS with CC.

We extracted data on ongoing pregnancy and clinical pregnancy. We defined ongoing pregnancy as a fetal heartbeat seen on ultrasound by 12 weeks of gestation and clinical pregnancy as a vital pregnancy seen on ultrasound. We registered all outcomes per woman. We extracted the mean EMT and SDs from the studies. In case the SE was provided, we calculated the SD (SD = SE $\times \sqrt{n}$). We used Review Manager software to calculate mean differences (MD) with 95% CIs using a fixed model. In case of statistical heterogeneity above an I^2 of 50%, we considered the random effect model as the primary model. We performed a meta-regression analysis to evaluate whether there were differences between the cohort studies and the randomized studies and to evaluate if the drugs interacted with the estimated effect of EMT. As no cut-off values for EMT were available, the pre-planned summary receiver operating characteristic (sROC) curve to assess the accuracy of EMT in the prediction of pregnancy could not be made (Reitsma *et al.*, 2005).

Results

The electronic search revealed 1563 articles, of which we selected 110 articles for full reading after screening the title and abstract. After reading the full text, we excluded 87 studies (Fig. 1). Checking of cross references revealed two other studies. The characteristics of the 23 included studies are listed in Table II. There were 17 RCTs and 6 cohort studies comprising a total of 3846 women.

The average quality of the studies was rated low to moderate.

The largest study included 446 women (De Geyter *et al.*, 2000) and the smallest study 30 women (Sipe *et al.*, 2006). Two studies reported live birth rates (Revelli *et al.*, 2006; Sipe *et al.*, 2006), five trials

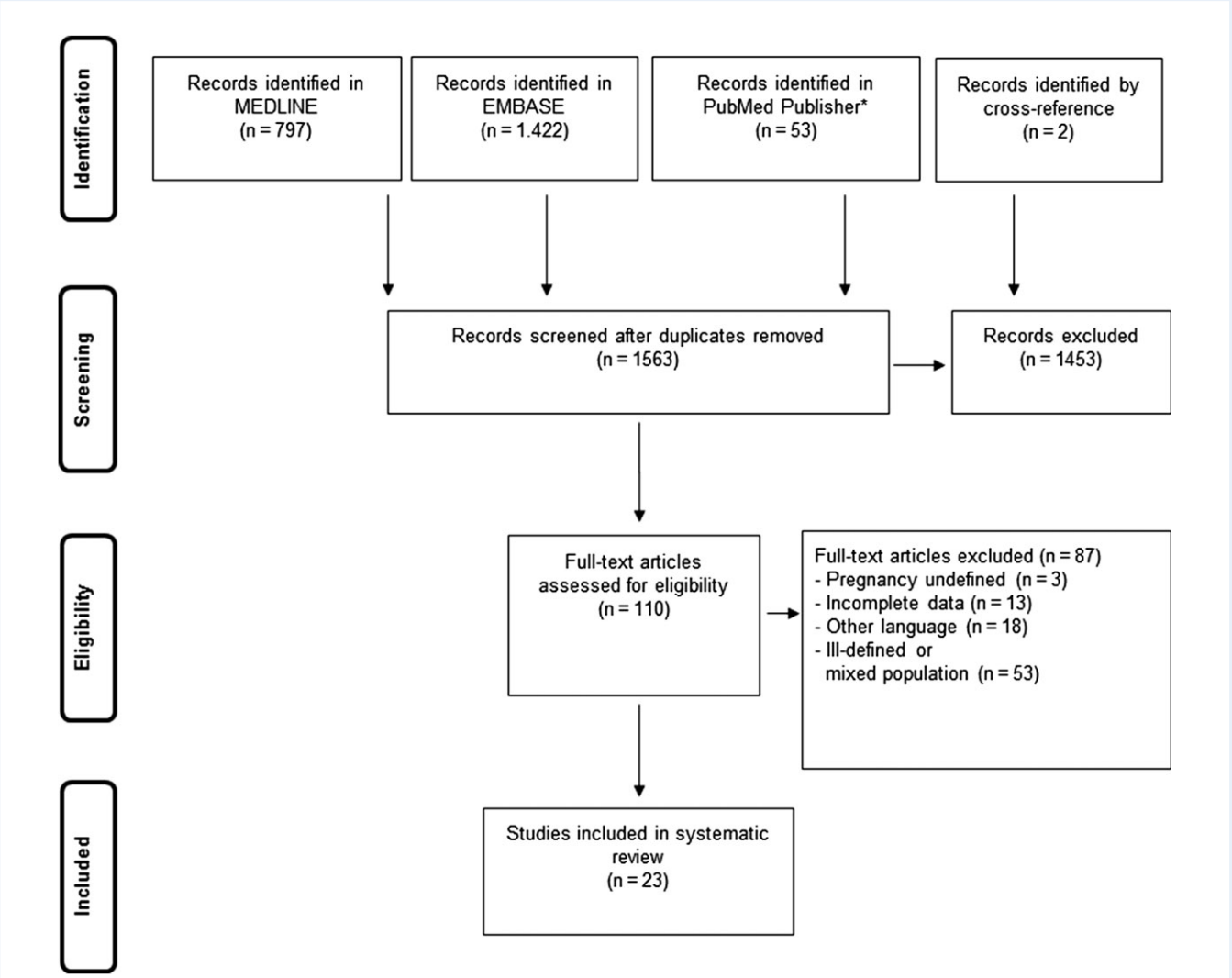

Figure 1 Flow chart of search and selection strategy for studies in a systematic review of endometrial thickness during IUI with ovarian stimulation. * We searched for citations recently added to PubMed via electronic submission from a publisher, and are soon to proceed to the next stage by adding the tag [sb].

Table II Characteristics of the included studies.

Author	Design	Subjects	No. of women	No. of cycles	EMT measurement day	Drug(s) group 1	EMT group 1 (mm, mean (SD))	Female age group 1 (years, mean (SD))	Drug(s) group 2	EMT group 2 (mean (SD))	Female age group 2 (mean (SD))
De Geyter *et al.* (2000)	Cohort	Unexplained + mild male	446	NA	Day of LH surge	uFSH	10.4 (2.2)	NA	NA	NA	NA
Tsai *et al.* (2000)	Cohort	Unexplained	110	110	Day of IUI	CC 50–100 mg/day + HMG	NA*	NA	NA	NA	NA
Mitwally and Casper (2003)**	Cohort	Unexplained + mild male	110	110	Day of HCG trigger	LET 2.5 mg/day + FSH	9.1 (2)	34.8 (4.2)	FSH	10 (2)	34.8 (4.5)
Esmailzadeh and Faramarzi (2007)	Cohort	Unexplained + mild male	249	562	Day of HCG trigger	CC 50–150 mg/day	NA*	NA	NA	NA	NA
Asante *et al.* (2013)	Cohort	Unexplained	131	280	Cycle day 10–11-12	CC 25–150 mg/day	NA*	NA	NA	NA	NA
Bensdorp *et al.* (2015)	Cohort	Unexplained + mild male	194	779	Day of HCG trigger	CC 100 mg/day	8.28 (2.46)	34 (3.67)	FSH	8.75 (1.96)	34 (3.67)
Sammour *et al.* (2001)	RCT	Unexplained	49	NA	Day of HCG trigger	CC 100 mg/day	6.9 (3)	32.8 (?)	LET 2.5 mg/day	8.6 (3)	30.7 (?)
Al-Fozan *et al.* (2004)	RCT	Unexplained	154	238	Day of HCG trigger	LET 7.5 mg/day	7.1 (0.2)	30.7 (0.5)	CC 100 mg/day	8.2 (0.6)	31.5 (0.5)
Barroso *et al.* (2006)	RCT	Unexplained	41	41	Day of HCG trigger	LET 2.5 mg/day + rFSH	9.5 (1.5)	32.5 (1.2)	CC 100 mg/day + rFSH	7.3 (1.1)	33.4 (1.0)
Baysoy *et al.* (2006)	RCT	Unexplained	80	76	Day of HCG trigger	LET 5 mg/day	8.91 (1.8)	27.2 (5.5)	HMG	10.05 (2.9)	28.1 (4.3)
Davar *et al.* (2006)	RCT	Unexplained + mild male	115	115	Unknown	LET 5 mg/day + rFSH	6.9 (2.5)	28.7 (2.9)	CC 100 mg/day + rFSH	7.6 (1.8)	25.7 (3.8)
Revelli *et al.* (2006)	RCT	Unexplained	184	184	Day of HCG trigger	uFSH	9.6 (1.9)	32.7 (4.3)	rFSH	9.5 (1.5)	32.7 (4.3)
Sipe *et al.* (2006)	RCT	Unexplained	30	NA	Cycle day 12–14	Anastrozole 1 mg/day + FSH	9.3 (2.3)	30 (4.5)	CC 100 mg/day + FSH	8.9 (2.9)	32 (3.3)
Akbary-Asbagh *et al.* (2007)***	RCT	Unexplained	132	132	Unknown	CC 100 mg/day + HMG	6.4 (0.8)	27.3 (3.3)	LET 5 mg/day + HMG	7.0 (1.1)	27 (4)
Gregoriou *et al.* (2008)	RCT	Unexplained	50	131	Day of HCG trigger	rFSH	8.6 (1.8)	31.5 (3.7)	LET 5 mg/day	7.1 (2.3)	32.1 (3.9)
Tehrani *et al.* (2008)	RCT	Unexplained	140	NA	Day of HCG trigger	LET 5 mg/day	9.7 (1.6)	32.8 (1.2)	CC 100 mg/day + HMG	7.8 (2.0)	33.3 (1.3)
Badawy *et al.* (2009)	RCT	Unexplained	412	804	Cycle day 10–12-14	LET 5 mg/day	9.3 (0.4)	29.1 (3.0)	CC 100 mg/day	9.2 (0.6)	28.3 (2.8)
Badawy *et al.* (2010)	RCT	Unexplained	280	434	Day of HCG trigger	CC 100 mg/day + HMG	8.9 (0.62)	27.3 (2.6)	LET 5 mg/day + HMG	9.1 (0.42)	28.3 (2.8)
	RCT		189	189		CC 100 mg/day	9.3 (1.2)	30.6 (5.1)	rFSH	9.6 (1.2)	30.0 (4.9)

Continued

Table II *Continued*

Author	Design	Subjects	No. of women	No. of cycles	EMT measurement day	Drug(s) group 1	EMT group 1 (mm, mean (SD))	Female age group 1 (years, mean (SD))	Drug(s) group 2	EMT group 2 (mean (SD))	Female age group 2 (mean (SD))
Berker *et al.* (2011)		Unexplained + mild male			Day of HCG trigger						
Fouda and Sayed (2011)	RCT	Unexplained	214	421	Day of HCG trigger	LET 2.5 mg/day	9.10 (1.84)	26.7 (3.5)	CC 100 mg/day	8.18 (1.93)	26.1 (3.2)
Akbari *et al.* (2012)	RCT	Unexplained	160	160	Day of HCG trigger	LET 5 mg/day + HMG	9.08 (1.2)	28.5 (4.7)	CC 100 mg/day + HMG	8.1 (1.9)	28.4 (4.5)
Ibrahim *et al.* (2012)	RCT	Unexplained	270	270	Day of HCG trigger	LET 2.5 mg/day	9.48 (0.3)	27.3 (3.0)	CC 100 mg/day	7.11 (0.21)	29.5 (3.0)
Zadehmodares *et al.* (2012)	RCT	Unexplained + mild male	106	NA	2–3 times during treatment	LET 5 mg/day + FSH	6.8 (1.5)	26.7 (3.4)	CC 100 mg/day + FSH	6.6 (1.2)	25.7 (4.6)

CC, clomiphene citrate; LET, letrozole; rFSH, recombinant FSH; uFSH, urinary FSH; EMT, endometrial thickness.
*Mean EMT was not available for the total treatment group, but only for the pregnant and non-pregnant women.
**The study of Mitwally and Casper (2003) contained a third treatment group: 18 women received CC+FSH; EMT for this group was (mean(SD)) 8.0 (2).
***The study of Akbary-Asbagh *et al.* (2007) contained a third treatment group: 28 women received HMG alone; EMT for this group was (mean(SD)) 7.3 (1.1).

reported pregnancy rates without defining the type of pregnancy, but since ultrasound findings were available we interpreted pregnancy outcomes as clinical pregnancy rates (Al-Fozan *et al.*, 2004; Barroso *et al.*, 2006; Akbary-Asbagh *et al.*, 2007; Badawy *et al.*, 2009, 2010). All other studies reported clinical pregnancy rates. Since ongoing pregnancy rates were not available, we used clinical pregnancy rates as the outcome measure.

In three studies data on EMT and pregnancy were available in the articles (Tsai *et al.*, 2000; Esmailzadeh and Faramarzi, 2007; Bensdorp *et al.*, 2015). We contacted the authors of the remaining studies to provide the missing data on the EMT in pregnant and non-pregnant women, and four of them were able to supply these data (De Geyter *et al.*, 2000; Revelli *et al.*, 2006; Fouda and Sayed, 2011; Asante *et al.*, 2013). Five of these seven studies were cohort studies and two were RCTs. We asked all authors if they could provide the number of pregnant and non-pregnant women above and below a certain EMT cut-off value. None of the studies could provide these data and therefore ROC curve analysis was not feasible. We cannot exclude that cycles were canceled when a low EMT was measured. We assume this was not common practice as none of the studies mentioned canceling a cycle on the basis of EMT.

In all 23 studies data on type of drug and EMT were available. Six of these studies were cohort studies of which two studies evaluated CC, one study evaluated uFSH and one study evaluated CC combined with HMG. One comparative cohort study compared CC with gonadotrophins, another compared letrozole plus FSH with FSH.

The other 17 studies were RCTs. One RCT compared CC with gonadotrophins, five compared CC with letrozole, eight compared CC plus gonadotrophins with letrozole (or anastrozole), two compared letrozole with gonadotrophins and one compared rFSH with uFSH. All studies used HCG-injections to trigger ovulation. Five studies used a form of luteal phase support, either by administering progesterone suppository or injections (Barroso *et al.*, 2006; Revelli *et al.*, 2006; Badaway *et al.*, 2009, 2010; Zadehmodares *et al.*, 2012).

EMT in pregnant versus non-pregnant women

The seven studies (two RCTs and five cohorts) from which we could extract mean EMT and corresponding SDs for pregnant and non-pregnant women are summarized in Table III. A total of 365 women became pregnant and 1160 women did not. Six studies found no statistical evidence of a difference between pregnant and non-pregnant women and one study observed a significantly thicker EMT in pregnant women (Esmailzadeh and Faramarzi, 2007). Women who conceived had on average a thicker EMT than women who did not conceive (MD: 0.48, 95% CI: 0.18 to 0.77; I^2 = 73%). Using a random effect model the difference was no longer statistically significant (MD: 0.51, 95% CI: −0.05 to 1.07; I^2 = 74%) (Fig. 2).

To overcome the statistical heterogeneity across studies, we also performed a sensitivity analysis leaving out the one study that found a significant difference between groups (Esmailzadeh and Faramarzi, 2007). The MD was not statistically significant (MD: 0.25, 95% CI: −0.05 to 0.56; I^2 = 0%) for pregnant versus non-pregnant women.

Meta-regression did not indicate any difference in findings between the two RCTs and five cohort studies (P = 0.41). There was also no indication of a difference between treatment groups (P = 0.79).

Table III EMT for pregnant and non-pregnant women.

Author	Design	Subjects	Drug(s)	Pregnancy per woman*	EMT (mm) pregnant women (mean (SD))	EMT (mm) non-pregnant women (mean (SD))
De Geyter *et al.* (2000)	Cohort	Unexplained + mild male	uFSH	92/446 (21%)	10.5	10.4
Tsai *et al.* (2000)	Cohort	Unexplained	CC+HMG	16/110 (15%)	12.1 (2.6)	11.0 (2.9)
Esmailzadeh and Faramarzi (2007)	Cohort	unexplained + mild male	CC	61/249 (25%)	10.1 (3.0)	7.7 (3.5)
Asante *et al.* (2013)	Cohort	Unexplained	CC	37/131 (28%)	7.05 (1.79)	6.98 (2.21)
Bensdorp *et al.* (2015)	Cohort	Unexplained + mild male	CC or FSH	76/194 (39%)	8.74 (2.38)	8.37 (2.54)
Revelli *et al.* (2006)	RCT	Unexplained	uFSH versus rFSH	19/184 (10%)	10.3 (3.1)	9.5 (2.9)
Fouda and Sayed (2011)	RCT	Unexplained	CC	24/105 (23%)	8.42 (1.5)	8.15 (1.98)
Fouda and Sayed (2011)	RCT	Unexplained	LET	40/106 (38%)	8.8 (1.65)	9.18 (1.88)

*Outcome is live birth for study of Revelli *et al.* (2006), outcome is clinical pregnancy for all other studies.

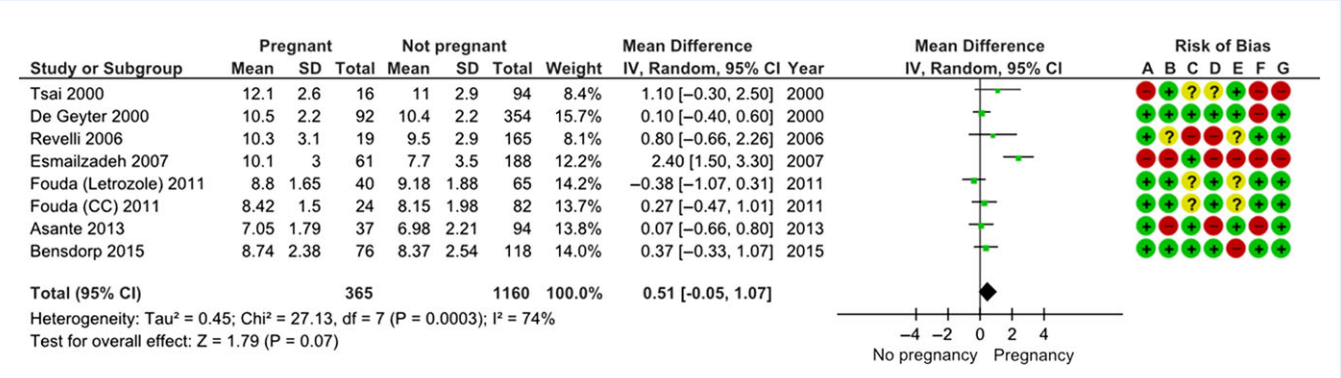

Figure 2 Endometrial thickness in pregnant versus non-pregnant women. EMT = endometrial thickness (mm). Red dots mean high risk of bias, yellow unclear risk of bias and green low risk of bias.

EMT for CC versus gonadotrophins

Pooling the data of one cohort study and one RCT that compared CC with gonadotrophins, suggested that women treated with CC had a slightly thinner EMT than women treated with gonadotrophins ($N = 383$, MD: −0.33, 95% CI: −0.64 to −0.01; $I^2 = 0\%$) (Fig. 3).

EMT for CC versus letrozole and CC plus gonadotrophins versus letrozole

We found five studies that compared CC and letrozole, all RCTs. The pooled data suggested that women treated with CC had a significantly thinner EMT than women treated with letrozole ($N = 1087$; MD: 1.14, 95% CI: 0.78–1.51; $I^2 = 86\%$). Using a random effect model the difference was no longer statistically significant (MD: −0.84, 95% CI: −1.97 to 0.28; $I^2 = 86\%$).

We found nine studies that compared CC plus gonadotrophins with letrozole, eight RCTs and one cohort. The pooled data suggested that women treated with the combination of CC plus gonadotrophins had a significantly thinner EMT than women treated with letrozole ($N = 1010$; MD: −0.78, 95% CI: −0.99 to −0.57; $I^2 = 84\%$).

Using a random effect model the difference was still statistically significant (MD: −0.79, 95% CI: −1.37 to −0.20; I^2: = 84%) (Fig. 4).

EMT for letrozole versus gonadotrophins

We found two studies that compared letrozole with gonadotrophins. Women treated with letrozole had a significantly thinner endometrium than women treated with gonadotrophins ($N = 130$; MD: −1.31, 95% CI: −2.08 to −0.53; $I^2 = 0\%$) (Fig. 5).

Discussion

In this meta-analysis we found no evidence for an association between EMT and pregnancy rates. Women treated with CC had a marginally thinner EMT than women treated with gonadotrophins. There was no evidence for a difference in EMT between CC and letrozole. The

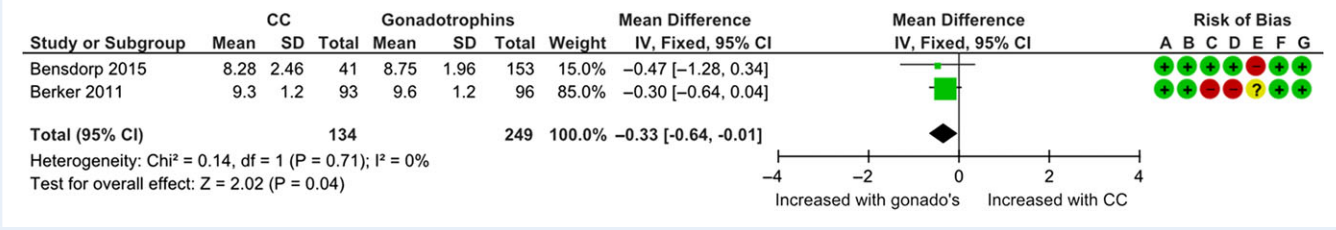

Figure 3 EMT for clomiphene citrate versus gonadotrophins. CC = clomiphene citrate.

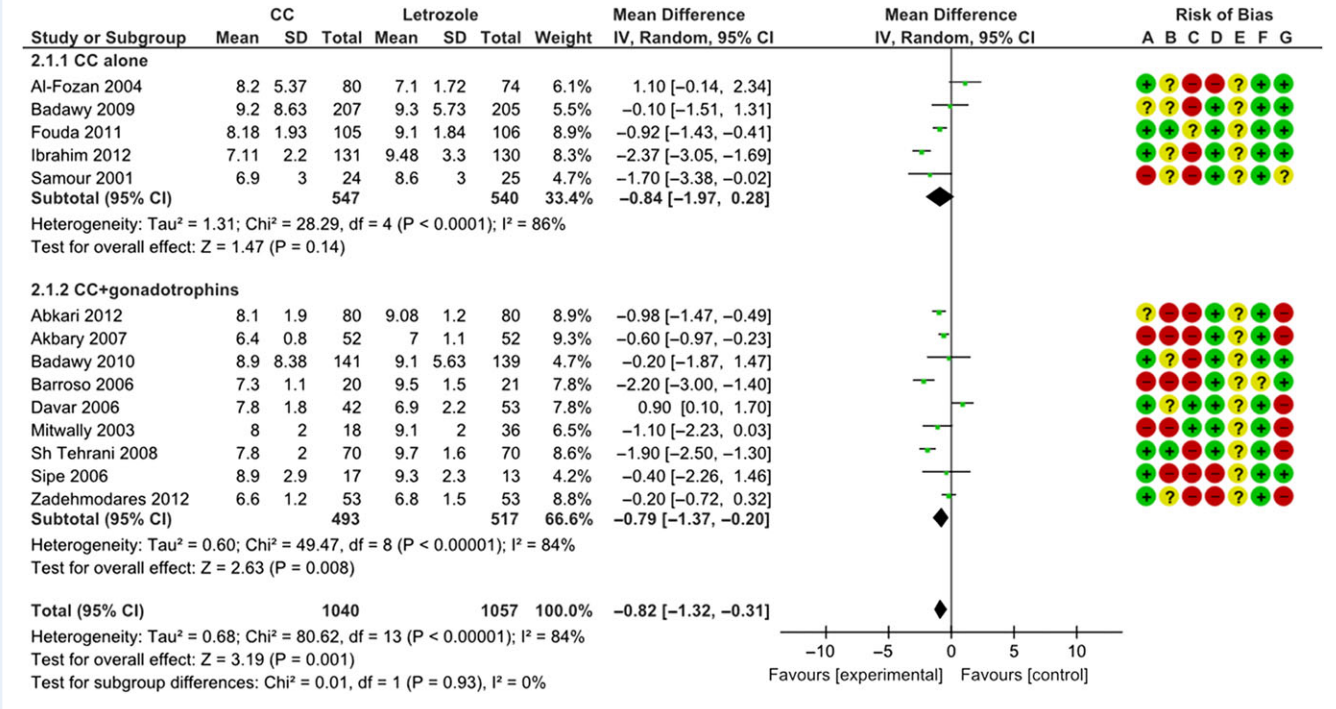

Figure 4 EMT for CC versus letrozole and CC plus gonadotrophins versus letrozole.

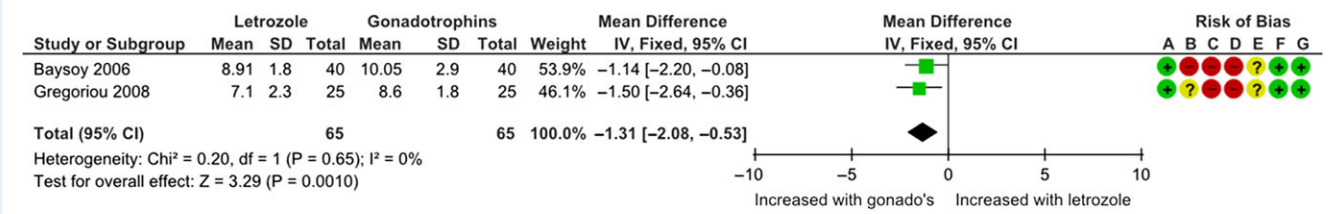

Figure 5 EMT for letrozole versus gonadotrophins.

combination of CC plus gonadotrophins resulted in a slightly thinner endometrium than letrozole, and letrozole alone resulted in a slightly thinner EMT than gonadotrophins alone.

Some limitations of this review need to be addressed. The average quality of the included studies was low to moderate and mean EMT values differed across studies resulting in considerable statistical heterogeneity. Furthermore, EMT was not a primary outcome in any of the studies. It seems likely that EMT had not been measured in all women. The number of missing values for this outcome was not reported in the included studies.

A limitation of our study is that the included studies did not report data on ongoing pregnancy rates and therefore we chose to use clinical pregnancy as outcome measure.

CC versus gonadotrophins, and letrozole versus gonadotrophins were compared in two studies only. Another limitation is the fact that we could not perform our planned sROC curve to determine the accuracy of EMT in the prediction of pregnancy, since the included studies did not deliver the necessary data.

Our review confirms the finding of one other review that evaluated EMT and pregnancy rates, but was limited to letrozole and CC cycles in women with unexplained subfertility (Liu *et al.*, 2014). An association between EMT and pregnancy had been noted previously in an IUI population (Dickey *et al.*, 1993a,b): None of the women in this study had a pregnancy at an EMT below 6 mm. This finding was not confirmed by a study in a similar IUI population published a few years later, as these authors found pregnancies occurring at the lowest measured EMT of 4 mm (Hock *et al.*, 1997).

The small differences in EMT that we found in relation to type of drug are counterintuitive. Biologically it seems possible that OS with gonadotrophins alone results in thicker endometrium than stimulation with CC and stimulation with letrozole whereas the combination of CC with gonadotrophins gives thinner EMT than letrozole. We cannot exclude that the observed differences in EMT are due to heterogeneity across the included studies. Also, previous studies have reported that there can be an interobserver variability in measuring EMT by transvaginal ultrasound with a MD: 1.5 mm (Karlsson *et al.*, 1994). The small but statistically significant differences of <1.5 mm in our meta-analyses therefore are likely to be irrelevant clinically.

In IVF, the impact of the thickness of the proliferated endometrium on pregnancy rates has been studied in a review pooling the results of 13 studies that showed that no pregnancies occurred if the EMT was below 5 mm (Friedler *et al.*, 1996). Based on the Friedler *et al.* (1996) review, the National Institute for Health and Care Excellence fertility guideline recommends not to transfer a fresh embryo when the EMT is <5 mm (NICE, 2013). A second, more recent systematic review pooling the results of 23 IVF studies, found that the chances of conception decreased if the EMT was ≤7 mm (odds ratio: 0.38, 95% CI: 0.09–1.5) compared to an EMT of over 7 mm (Kasius *et al.*, 2014).

We can only speculate why a thin endometrium is clinically more relevant in IVF cycles than in IUI. Possibly a thin endometrium developing under maximal OS conditions implies genuine diminished implantation potential compared to a thinner endometrium developing under milder stimulation conditions, as with IUI.

Since embryos do not develop well in high oxygen tensions, IVF laboratories keep oxygen concentrations around 5%. In endometrium of <7 mm, the functional layer is thin or absent, which causes the embryo to be closer to the uterine spiral arteries. This highly vascular layer may cause high oxygen concentrations in the basal endometrium and thus high oxygen concentrations too close to the implanting embryo (Casper, 2011). A mere theoretical explanation could be that embryos developing *in vivo* are less susceptible to this higher oxygen exposure compared to embryos developing *in vitro* and thus, in IUI–OS, this effect is of less importance.

As the EMT does not seem to be a predictor for success in IUI–OS, it might be desirable to examine other biomarkers. It has been suggested that the subendometrial neovascularization measured by three-dimensional power Doppler ultrasound (3D PD-US) can predict pregnancy in women undergoing IUI. In a prospective study of 106 women undergoing ovulation induction and IUI, color Doppler ultrasound and a 3D PD-US examination were performed on the day of insemination. Pregnant women had higher endometrial and subendometrial blood flow parameters than women who did not conceive. Pregnancies did not occur when endometrial blood flow was not detected (Kim *et al.*, 2010). Another possible biomarker is the activin A concentration in uterine washing fluid. In a retrospective case-control study of 50 women treated with IUI–OS with FSH, pregnant women had significantly higher levels of activin A than non-pregnant women (Florio *et al.*, 2010). However before these new techniques are implemented, future research must clarify if 3D PD-US and measuring activing A levels is helpful in monitoring IUI–OS cycles.

Our results suggest that the differences in EMT between women who get pregnant and those that do not are too small to be useful as a tool to guide treatment for the individual woman. Therefore, canceling IUI cycles with thin endometrial lining because of the presumed negative effect of the thin EMT—of which we have found no proof—may lead to the very effect one tries to avoid, i.e. non-conception by the simple and easy to understand mechanism of not inseminating.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgments

The authors thank the corresponding authors of the studies included this paper for their response to the requests for additional information.

Authors' roles

M.v.V. and N.W. selected studies, performed data extraction and statistical analysis and took the lead in writing the article. J.L. performed the literature search. M.v.W. provided statistical support and performed the meta-regression analysis. All authors took part in writing and revising several drafts of the article.

Funding

No funding was received for conducting this review.

Conflict of interest

None of the authors has any conflict of interests to report.

References

Akbari S, Ayazi Roozbahani M, Ayazi Roozbahani F. Comparing of letrozole versus clomiphene citrate combined with gonadotropins in intrauterine insemination cycles. *Iran J Reprod Med* 2012;**10**:29–32.

Akbary-Asbagh F, Heidar Z, Frozan-Fard F, Nouri K, Azmodeh O, Ghasemynejad A, Salsabily N. Amirian. Evaluation of letrozole therapeutic effect in infertile women. *Acta Medica Iranica* 2007;**45**:199–203.

Al-Fozan H, Al-Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004;**82**:1561–1563.

Asante A, Coddington CC, Schenck L, Stewart EA. Thin endometrial stripe does not affect likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles. *Fertil Steril* 2013;**100**:1610–4 e1.

Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial. *Fertil Steril* 2009;**92**:1355–1359.

Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: a prospective randomised trial. *J Obstet Gynaecol* 2010;**30**:617–621.

Barroso G, Menocal G, Felix H, Rojas-Ruiz JC, Arslan M, Oehninger S. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate as adjuvants to recombinant follicle-stimulating hormone in controlled ovarian hyperstimulation: a prospective, randomized, blinded clinical trial. *Fertil Steril* 2006;**86**:1428–1431.

Baysoy A, Serdaroglu H, Jamal H, Karatekeli E, Ozornek H, Attar E. Letrozole versus human menopausal gonadotrophin in women undergoing intrauterine insemination. *Reprod Biomed Online* 2006;**13**:208–212.

Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM, Koks CA, Oosterhuis GJ, Hoek A, Hompes PG, Broekmans FJ, Verhoeve HR, de Bruin JP, van Golde R. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *Br Med J* 2015;**350**:g7771.

Berker B, Kahraman K, Taskin S, Sukur YE, Sonmezer M, Atabekoglu CS. Recombinant FSH versus clomiphene citrate for ovarian stimulation in couples with unexplained infertility and male subfertility undergoing intrauterine insemination: a randomized trial. *Arch Gynecol Obstet* 2011;**284**:1561–1566.

Casper RF. It's time to pay attention to the endometrium. *Fertil Steril* 2011;**96**:519–521.

De Geyter C, Schmitter M, De Geyter M, Nieschlag E, Holzgreve W, Schneider HP. Prospective evaluation of the ultrasound appearance of the endometrium in a cohort of 1,186 infertile women. *Fertil Steril* 2000;**73**:106–113.

Dehbashi S, Parsanezhad ME, Alborzi S, Zarei A. Effect of clomiphene citrate on endometrium thickness and echogenic patterns. *Int J Gynaecol Obstet* 2003;**80**:49–53.

Davar R, Tayebi N, Asgharnia M, Aflatoonian A. Comparison of the use of letrozole and clomiphene citrate in regularly ovulating women undergoing intrauterine insemination. *Middle East Fertil Soc J* 2006;**11**:113–118.

Dickey RP, Olar TT, Taylor SN, Curole DN, Harrigill K. Relationship of biochemical pregnancy to pre-ovulatory endometrial thickness and pattern in patients undergoing ovulation induction. *Hum Reprod* 1993a;**8**:327–330.

Dickey RP, Olar TT, Taylor SN, Curole DN, Matulich EM. Relationship of endometrial thickness and pattern to fecundity in ovulation induction cycles: effect of clomiphene citrate alone and with human menopausal gonadotropin. *Fertil Steril* 1993b;**59**:756–760.

Esmailzadeh S, Faramarzi M. Endometrial thickness and pregnancy outcome after intrauterine insemination. *Fertil Steril* 2007;**88**:432–437.

Florio P, Bruni L, Galleri L, Reis FM, Borges LE, Bocchi C, Litta P, De Leo V, Petraglia F. Evaluation of endometrial activin A secretion for prediction of pregnancy after intrauterine insemination. *Fertil Steril* 2010;**93**:2316–2320.

Fouda UM, Sayed AM. Extended letrozole regimen versus clomiphene citrate for superovulation in patients with unexplained infertility undergoing intrauterine insemination: a randomized controlled trial. *Reprod Biol Endocrinol* 2011;**9**:84.

Friedler S, Schenker JG, Herman A, Lewin A. The role of ultrasonography in the evaluation of endometrial receptivity following assisted reproductive treatments: a critical review. *Hum Reprod Update* 1996;**2**:323–335.

Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. *Hum Reprod* 1990;**5**:670–674.

Gregoriou O, Vlahos NF, Konidaris S, Papadias K, Botsis D, Creatsas GK. Randomized controlled trial comparing superovulation with letrozole versus recombinant follicle-stimulating hormone combined with intrauterine insemination for couples with unexplained infertility who had failed clomiphene citrate stimulation and intrauterine insemination. *Fertil Steril* 2008;**90**:678–683.

Haritha S, Rajagopalan G. Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. *Int J Gynaecol Obstet* 2003;**81**:287–292.

Hock DL, Bohrer MK, Ananth CV, Kemmann E. Sonographic assessment of endometrial pattern and thickness in patients treated with clomiphene citrate, human menopausal gonadotropins, and intrauterine insemination. *Fertil Steril* 1997;**68**:242–245.

Ibrahim MI, Moustafa RA, Abdel-Azeem AA. Letrozole versus clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. *Arch Gynecol Obstet* 2012;**286**:1581–1587.

Isaacs JD Jr, Wells CS, Williams DB, Odem RR, Gast MJ, Strickler RC. Endometrial thickness is a valid monitoring parameter in cycles of ovulation induction with menotropins alone. *Fertil Steril* 1996;**65**:262–266.

Karlsson B, Granberg S, Ridell B, Wikland M. Endometrial thickness as measured by transvaginal ultrasonagraphy: interobserver variation. *Ultrasound Obstet Gynecol* 1994;**4**:320–325.

Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC, Broekmans FJ. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. *Hum Reprod Update* 2014;**20**:530–541.

Kim A, Han JE, Yoon TK, Lyu SW, Seok HH, Won HJ. Relationship between endometrial and subendometrial blood flow measured by three-dimensional power Doppler ultrasound and pregnancy after intrauterine insemination. *Fertil Steril* 2010;**94**:747–752.

Kolibianakis EM, Zikopoulos KA, Fatemi HM, Osmanagaoglu K, Evenpoel J, Van Steirteghem A, Devroey P. Endometrial thickness cannot predict ongoing pregnancy achievement in cycles stimulated with clomiphene citrate for intrauterine insemination. *Reprod Biomed Online* 2004;**8**:115–118.

Liu A, Zheng C, Lang J, Chen W. Letrozole versus clomiphene citrate for unexplained infertility: a systematic review and meta-analysis. *J Obstet Gynaecol Res* 2014;**40**:1205–1216.

Mitwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Hum Reprod* 2003;**18**:1588–1597.

Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H. Effects of clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. *Fertil Steril* 1997;**67**:256–260.

NICE. *Fertility: Assessment and Treatment for People with Fertility Problems*. 2013.

Ombelet W, Cooke I, Dyer S, Serour G, Devroey P. Infertility and the provision of infertility medical services in developing countries. *Hum Reprod Update* 2008;**14**:605–621.

Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**:982–990.

Reuter KL, Cohen S, Furey L, Baker S. Sonographic appearance of the endometrium and ovaries during cycles stimulated with human menopausal gonadotropin. *J Reprod Med* 1996;**41**:509–514.

Revelli A, Poso F, Gennarelli G, Moffa F, Grassi G, Massobrio M. Recombinant versus highly-purified, urinary follicle-stimulating hormone (r-FSH vs. HP-uFSH) in ovulation induction: a prospective, randomized study with cost-minimization analysis. *Reprod Biol Endocrinol* 2006;**4**:38.

Sammour ABM, Tan SL, Tulandi T. Prospective randomized trial comparing the effects of letrozole (LE) and clomiphene citrate (CC) on follicular development, endometrial thickness and pregnancy rate in patients undergoing super-ovulation prior to intrauterine insemination (IUI). *Fertil Steril* 2001;**76**:S110. (ASRM abstracts).

Sipe CS, Davis WA, Maifeld M, Van Voorhis BJ. A prospective randomized trial comparing anastrozole and clomiphene citrate in an ovulation induction protocol using gonadotropins. *Fertil Steril* 2006;**86**: 1676–1681.

Sterne JAC, Hernán MA, Reeves BC, on behalf of the development group for ROBINS-I. ROBINS-I: a tool for assessing Risk Of Bias In Non-randomized Studies of Interventions, Version 5 July 2016. *Br Med J* 2016;**355**:4919–4927.

Tehrani Nejad E, Abediasl Z, Rashidi BH, Azimi Nekoo E, Shariat M, Amirchaghmaghi E. Comparison of the efficacy of the aromatase inhibitor letrozole and clomiphene citrate gonadotrophins in controlled ovarian hyperstimulation: a prospective, simply randomized, clinical trial. *J Assist Reprod Genet* 2008;**25**:187–190.

Tsai HD, Chang CC, Hsieh YY, Lee CC, Lo HY. Artificial insemination. Role of endometrial thickness and pattern, of vascular impedance of the spiral and uterine arteries, and of the dominant follicle. *J Reprod Med* 2000;**45**:195–200.

Warrington C, Faraj R, Willett M. Endometrial thickness and outcome in sub-fertile women treated with clomiphene citrate. *J Obstet Gynaecol* 2008;**28**:626–628.

Zadehmodares S, Niyakan M, Sharafy SA, Yazdi MH, Jahed F. Comparison of treatment outcomes of infertile women by clomiphene citrate and letrozole with gonadotropins underwent intrauterine insemination. *Acta Med Iran* 2012;**50**:18–20.