

Among women undergoing embryo transfer, is the probability of pregnancy and live birth improved with ultrasound guidance over clinical touch alone? A systemic review and meta-analysis of prospective randomized trials

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Objective: To investigate the theory that ultrasound guidance during ET improves clinical outcomes.

Design: Systematic review of prospective, randomized, controlled trials comparing ultrasound with clinical touch methods of embryo catheter guidance.

Setting: Infertility centers.

Patient(s): 5,968 ET cycles in women.

Intervention(s): Embryo transfer with or without ultrasound guidance.

Main Outcome Measure(s): Meticulous electronic (e.g., PubMed, EMBASE, CENTRAL) and hand searches were performed to locate trials. Primary outcome measures were the live-birth, ongoing pregnancy, and clinical pregnancy rates. Secondary outcome measures were the implantation, multiple pregnancies, and miscarriage rates. In addition, the incidences of ectopic pregnancies and difficult transfers were evaluated.

Result(s): Twenty-five studies were retrieved, of which five were excluded. Meta-analysis of the remaining studies (5,968 ET cycles in women) was conducted by using the Mantel-Haenszel method (fixed-effect model).

There was a significantly increased chance of a live birth (odds ratio [OR] = 1.78, 95% confidence interval [CI] = 1.19 to 2.67), ongoing pregnancy (OR = 1.51, 95% CI = 1.31 to 1.74), clinical pregnancy (OR = 1.50, 95% CI = 1.34 to 1.67), embryo implantation (OR = 1.35, 95% CI = 1.22 to 1.50), and easy transfer rates after ultrasound guidance (OR = 0.68, 95% CI = 0.58 to 0.81). There was no difference in multiple pregnancy, ectopic pregnancy, or miscarriage rates.

Conclusion(s): Ultrasound-guided ET significantly increases the chance of live birth and ongoing and clinical pregnancy rates compared with the clinical touch method. (Fertil Steril® 2007;88:333–41. ©2007 by American Society for Reproductive Medicine.)

Key Words: Ultrasound-guided ET, clinical touch ET, meta-analysis, in vitro fertilization

Despite the major advancements made in ovarian stimulation protocols and in vitro embryo development, the pregnancy and embryo implantation rates after ET have remained relatively low. The majority of patients undergoing IVF will reach the transfer stage, with good-quality embryos available for transfer, but only a small proportion of them will ever achieve a clinical pregnancy, an ongoing pregnancy, or a live birth. It is estimated that up to 85% of the embryos

replaced into the uterine cavity will fail to implant (1). This makes the ET procedure a highly vital and, at the same time, highly inefficient step in IVF. Consequently, any modification to the standard protocol that will improve the outcomes is of great value.

The pregnancy rate after ET is dependent on multiple factors including embryo quality, endometrial receptivity, and the technique of the ET itself (2). In recent years, more stress has been placed on optimizing and standardizing the ET protocol. Factors such as ease of the procedure (3), catheter choice (4, 5), and dummy ET (6) have proved to improve the clinical outcomes.

Today, more than 25 years after the first reports of the beneficial effect of ultrasound guidance during the “blind” ET procedure were published (7, 8), the routine use of

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ultrasonography to guide the intrauterine ET catheter placement still is debated highly. This has been fueled by the conflicting results of published clinical trials, with some concluding that ultrasound guidance improves the clinical pregnancy and implantation rates and others reporting no such improvement in their results. In light of this controversy, and the need to identify clearly the relative efficacy of ultrasound guidance during ET, we decided to locate, analyze, and review systematically the best available evidence today for the use of ultrasonography during ET.

MATERIALS AND METHODS

Criteria for Considering Studies for This Review

All published, unpublished, and ongoing randomized trials reporting data that compare outcomes for women undergoing ET through the cervical route after IVF, or ICSI, using ultrasound-guided versus the clinical touch method were sought in all languages.

Types of Outcome Measures

The primary outcome measures were the live-birth, ongoing pregnancy, and clinical pregnancy rates. The secondary outcomes were the implantation, multiple pregnancies, and miscarriage rates. In addition, the incidences of ectopic pregnancies, difficult or failed transfers, and need for instrumental assistance during the transfer (e.g., stylette, tenaculum, dilatation, sounding), were evaluated. Last, the tips of the posttransfer catheters were evaluated for signs of cervical or endometrial trauma (e.g., presence of blood, mucus, or both), in addition to retained embryos.

Search Strategy for Identification of Studies

Meticulous computerized searches (last performed July 2006) were conducted by using MEDLINE (1966 to present); EMBASE (1980 to present); the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library issue 3, 2006; the National Research Register; the trial register of controlled trials (www.controlled-trials.com); the Latin American and Caribbean Health Sciences Literature database (LILACS); and details on reviews in progress collected by the National Health Service Centre for Reviews and Dissemination. Furthermore, the reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (e.g., European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine), and included studies were examined to identify additional relevant citations. Finally, ongoing and unpublished trials were sought by contacting experts in the field and commercial entities.

Methods of the Review

A standardized data extraction form was developed and pilot tested for consistency and completeness. Trials were considered for inclusion, and trial data extracted. Data management and statistical analyses were conducted by using the Review Manager 4.2, Meta-analysis With Interactive Explanations

1.2, and Power and Sample Size Calculations 2.1.30 statistical software packages.

Individual outcome data were included in the analysis if they met the prestated criteria. Where possible, data were extracted to allow for an intention-to-treat analysis, defined as including in the denominator all randomized cycles. If data from the trial reports were insufficient or missing, the investigators of individual trials were contacted via E-mail for additional information, to perform analyses on an intention-to-treat basis. A response was received from the correspondence authors of nine trials (9–17), with two providing the unpublished live-birth rates (11, 14).

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Statistical heterogeneity of the included studies was determined by visual inspection of the outcome tables and more formally by using the χ^2 and I^2 tests for heterogeneity.

The I^2 test is a statistical measure used to identify and quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (18). An I^2 value greater than 50% may be considered to represent substantial heterogeneity.

Meta-analysis of binary data was performed with the Mantel-Haenszel method and a fixed-effect model, and the odds ratio (OR) and 95% confidence intervals (95% CI) evaluated. Subsequently a sensitivity analysis was conducted by using the random-effects model. Furthermore, where appropriate, subgroup analyses were performed.

Search Results

A total of 25 prospective randomized controlled trials were identified (13 full-text papers, 11 conference abstracts, and one unpublished study) (Fig. 1). Of these, three studies (19–21) were excluded initially for duplicate publication (i.e., published as abstract in a conference proceeding and as full text in a peer-reviewed journal). In addition, two trials (10, 12) were excluded because no data were available for review. Finally, the methodologic quality of the remaining 20 trials was assessed and data extracted to allow for an intention-to-treat analysis (Table 1).

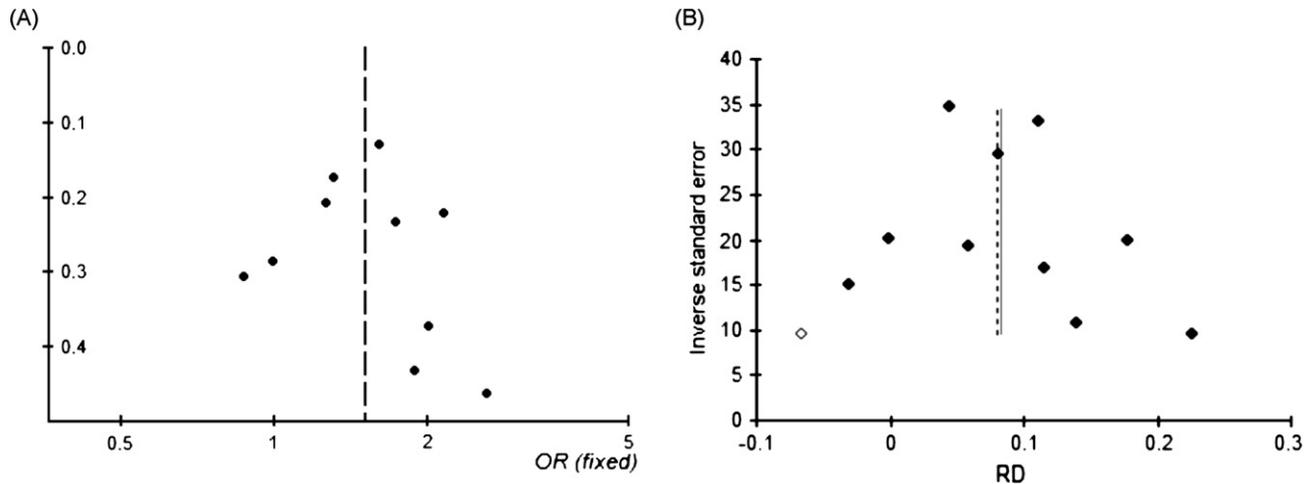
RESULTS

Primary Outcome Measures

With regard to the primary outcome measures, there was a significantly increased chance of a live birth (ultrasonography: 76/305 vs. clinical touch: 49/310, OR = 1.78, 95% CI = 1.19 to 2.67), an ongoing pregnancy (ultrasonography: 656/1,902 vs. clinical touch: 557/2,065, OR = 1.51, 95% CI = 1.31 to 1.74), and clinical pregnancy (ultrasonography: 1086/2,941 vs. clinical touch: 884/3,027, OR = 1.50, 95% CI = 1.34 to 1.68) with ultrasound guidance than with the standard clinical touch method (Figs. 2–4). Moreover, subgroup analyses of only the truly randomized trials, fresh non-donor cycles, and the frozen embryo replacement cycles

FIGURE 1

(A) Funnel and (B) “trim and fill” plots for ongoing pregnancy rates. RD = risk difference.



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revealed similar results (Table 2). Even so, patients undergoing oocyte donor cycles did not demonstrate any significant findings between the ultrasound-guided and the clinical touch groups. Nevertheless, it is important to note that only one trial used oocyte donor cycles.

Secondary Outcome Measures

As for the secondary outcome measures, there was a significant increased chance of embryo implantation after ultrasound guidance compared with the standard clinical touch method (ultrasonography: 974/5,662 vs. clinical touch: 810/5,841, OR = 1.35, 95% CI = 1.22 to 1.50). Even so, there were similar rates of multiple pregnancies, ectopic pregnancies, and spontaneous miscarriages in the two groups ($P > .05$).

As for the ease of transfer and the need for instrumental assistance, there was a statistically significant increased chance of having a difficult transfer, need for instrumental assistance, and failure to transfer with the assigned catheter during clinical touch alone compared with ultrasound guidance (Table 2). Even so, there was significant heterogeneity between the study trials: ease of transfer ($\chi^2 = 53.06$, $I^2 = 83.0\%$, $P < .00001$); need for instrumental assistance ($\chi^2 = 57.83$, $I^2 = 89.6\%$, $P < .00001$); failure to transfer with the assigned catheter ($\chi^2 = 2.92$, $I^2 = 65.8\%$, $P < .09$). Therefore, a series of sensitivity analyses were undertaken. The results of these analyses could only confirm the increased usage of instrumental assistance with the clinical touch group compared with the ultrasound-guided group ($P = .04$). The remaining comparisons could not be verified.

Finally, the catheter tips were evaluated for the presence of blood, mucus, and/or retained embryos. There were no significant differences for these rates between the two groups with

the exception of increased incidence of finding blood on the catheter tips after clinical touch ET.

DISCUSSION

Although most patients who undergo assisted procreation, via IVF or ICSI, will reach the ET stage with good-quality embryos available for replacement, embryo implantation remains the rate-limiting step in the success of this form of therapy. The aim of the ET procedure is to place embryos atraumatically and accurately within the uterus to allow for proper implantation and fetal development. Studies have shown that different factors may be involved in a successful transfer. These include ET catheter choice (4, 5), the use of ultrasound guidance (35, 36), the experience of the physician (37), the ease of the procedure (3), the presence or absence of blood on the catheter (38), the use of cervical introducers or obturators (39), the value of resting after transfer (40), the position of embryo insertion in the uterus (41, 42), and retention of embryos in the catheter (43).

To ascertain the importance of each step involved in the ET procedure, individual factors must be evaluated independently. Therefore, the ET procedure may be divided arbitrarily into four distinct sections: [1] preparation before ET (e.g., patient position, cervical preparation, uterine position, and the dummy ET); [2] technical aspects related to the ET catheter (e.g., catheter type and catheter loading); [3] the ET procedure (e.g., the site of embryo deposition within the uterus and techniques to assist with the accurate placement of the embryo within the uterus); and [4] posttransfer aspects (e.g., expulsion of fluid/embryos from the cervix after ET and bed rest after ET) (44). Because it would be difficult to compare several factors accurately at the same time, we decided to concentrate on one factor, the beneficial value of

TABLE 1

Review table of the included studies, comparing ultrasound-guided ET with clinical touch ET.

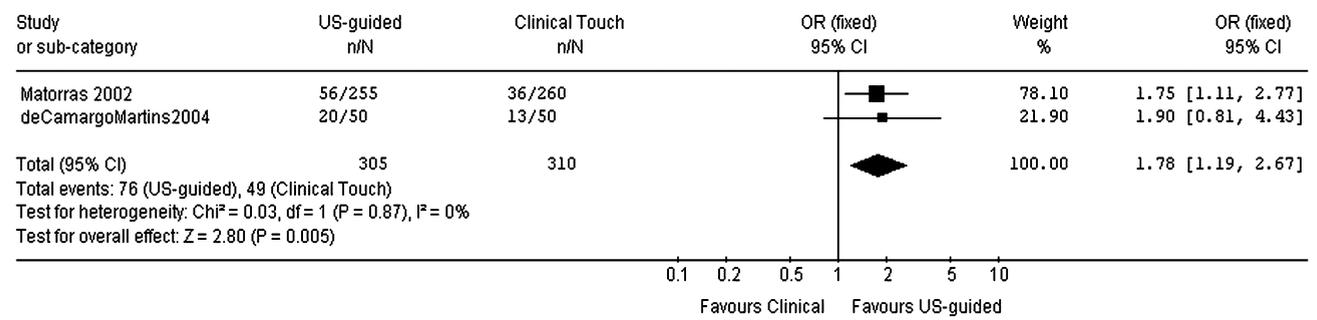
Included studies	Patients	ET cycles	A-priori sample size calculation	Method of randomization	Method of randomization concealment	Intention-to-treat	Follow-up	Confounders
Abdelmassih et al. (22)	NA	39	Not performed	Unclear	Unclear	ITT	CPR	Present—multiple catheters
Al-Shawaf et al. (9)	NA	241	Not performed	Availability of ultrasonographer	Inadequate	ITT	CPR	Multiple studies
Bar Hava et al. (23)	NA	131	Not performed	Unclear	Unclear	ITT	CPR	Not evident
Coroleu et al. (24)	362	362	Not performed	Computer-generated randomization table	Unclear	ITT	OPR	Not evident
Coroleu et al. (25)	184	184	Performed	Computer-generated randomization table	Unclear	ITT	OPR	Not evident
de Camargo Martins et al. (11)	100	100	Not performed	Computer-generated randomization table	Unclear	ITT	LBR	Not evident
Garcia-Velasco et al. (13)	374	374	Performed	Random permuted blocks	Adequate	ITT	OPR	Multiple physicians
Kan et al. (26)	195	195	Not performed	Availability of ultrasonographer	Inadequate	ITT	CPR	Multiple physicians
Kosmas et al. (27)	196	196	Not performed	Computer-generated randomization table	Unclear	Not ITT	OPR	Present—multiple catheters
Li et al. (28)	330	330	Not performed	Unclear	Unclear	ITT	CPR	Not evident
Maldonado et al. (29)	26	26	Not performed	Unclear	Unclear	ITT	CPR	Not evident
Marconi et al. (30)	83	83	Not performed	Unclear	Unclear	ITT	OPR	Multiple catheters
Matorras et al. (14)	515	515	Not performed	Computer-generated randomization table	Unclear	ITT	LBR	Not evident
Morago-Sanchez et al. (31)	67	67	Not performed	Unclear	Unclear	ITT	CPR	Multiple studies
Prapas et al. (32)	NA	132	Not performed	Alternate randomization	Inadequate	ITT	CPR	Not evident
Prapas et al. (15)	917	1,069	Not performed	Alternate randomization	Inadequate	ITT	CPR	Not evident
Sallam et al. (33)	539	640	Not performed	Alternate randomization	Inadequate	ITT	CPR	Not evident
Tang et al. (16)	800	800	Performed	Computer-generated randomization table	Adequate	ITT	OPR	Multiple physicians
Weissman et al. (33)	155	155	Not performed	Unclear	Unclear	ITT	CPR	Not evident
Wisanto et al. (34)	200	200	Not performed	Computer-generated randomization table	Unclear	Not ITT	CPR	Multiple studies, physicians

Note: ITT = intention to treat analysis performed; CPR = clinical pregnancy rate; OPR = ongoing pregnancy rate; LBR = live-birth rate.

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FIGURE 2

Meta-analysis forest plots showing live-birth rate following ultrasound-guided versus clinical touch ET.
US = ultrasound.



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ultrasound guidance to guide catheter placement during the ET procedure.

All the studies retrieved from our search have examined the role of two-dimensional (2-D) transabdominal ultrasound guidance during ET. Even so, vaginal ultrasound-guided ET (40, 45), as well as the use of three-dimensional (46) and fourth-dimensional ultrasound-guided ET have been reported. Nonetheless, it is important to mention that to the best of our knowledge there are no randomized controlled trials comparing any of these new modalities either with the standard clinical touch method or with the 2-D ultrasound-guided method.

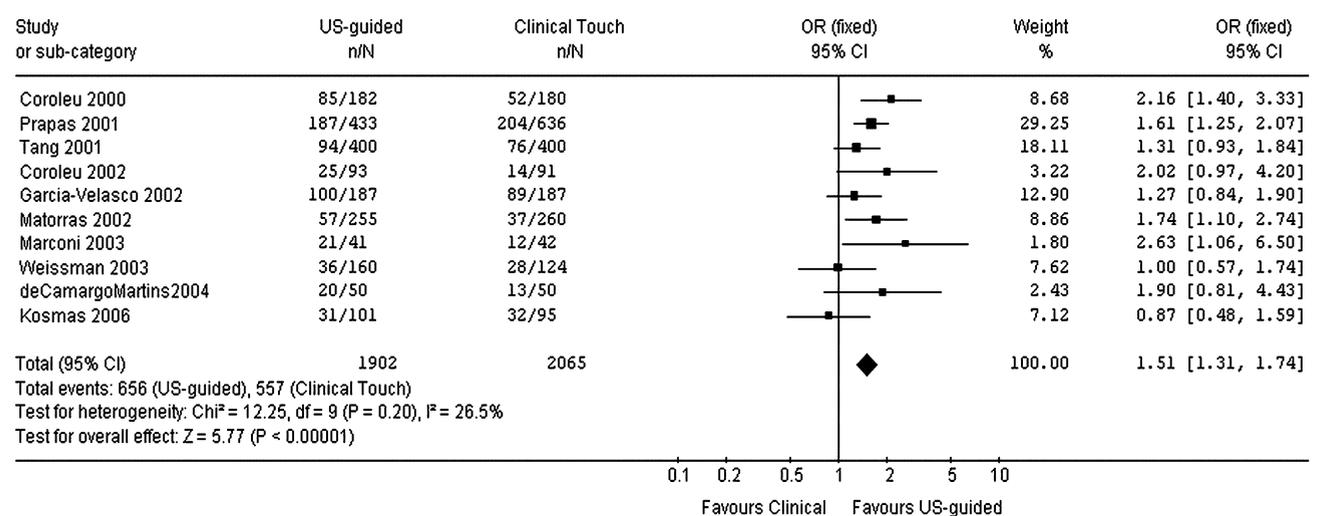
Systematic reviews and meta-analysis of randomized controlled trials have proved to be the highest level of evidence in

the hierarchy of medical knowledge. Even so, publication and search biases may confound the results of any systemic review, because studies showing positive results are more likely to be published (47, 48). Therefore, every effort has been made to avoid bias by searching a wide variety of online databases (with no language barriers), hand searching of the gray literature, and contacting commercial entities in search of unpublished or ongoing trials. The objective was to minimize the chance of publication or selection bias to strengthen the validity of the results of the systematic review. Failure to identify trials reported in conference proceedings might affect the results or threaten the validity of a systematic review (49).

In addition, multiple methods were used to detect publication, location, or selection biases including funnel plot, trim

FIGURE 3

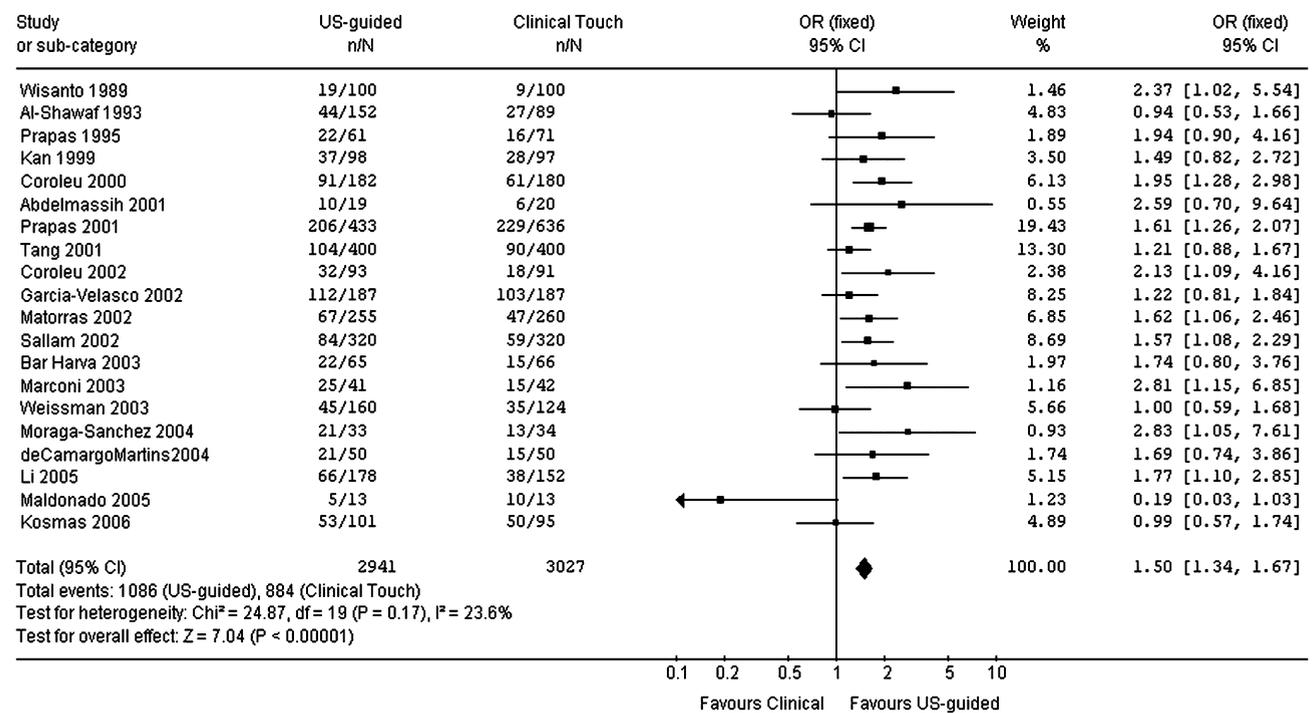
Meta-analysis forest plots showing ongoing pregnancy rate following ultrasound-guided versus clinical touch ET.
US = ultrasound.



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FIGURE 4

Meta-analysis forest plots showing clinical pregnancy rate following ultrasound-guided versus clinical touch ET. US = ultrasound.



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and fill funnel plot, and the Egger regression analyses (50). The funnel plot is a graphic display of study precision plotted against the effect size. It is used to investigate whether there is a link between study size and treatment effect. The funnel plot of the included studies shows asymmetry that may be due to publication bias. Even so, it is important to note that there may be other etiologies for the asymmetry found in funnel plot, including selection biases (e.g., location biases, language bias, citation bias, multiple publication bias), poor methodologic quality of smaller studies (e.g., poor methodologic design, inadequate analysis, fraud), true heterogeneity (i.e., size of effect differs according to study size), artifactual, and just by chance (51).

Duval and Tweedie (52) have proposed the “trim and fill” method for defining the extent of publication bias. It is based on adding studies to a funnel plot so that it becomes symmetrical. Then the smaller studies are omitted until the funnel plot is symmetrical (trimming). The trimmed funnel plot is used to estimate the true “center” of the funnel, and then the omitted studies and their missing “counterparts” around the center are replaced (filling). This provides an estimate of the number of missing studies and an adjusted treatment effect, including the “filled” studies.

Funnel plots, plots of the trials’ effect estimates against sample size, are skewed and asymmetric in the presence of

publication bias and other biases. Funnel plot asymmetry, measured by regression analysis, predicts discordance of results when meta-analyses are compared with single large trials. One of the commonly used regression methods is the Egger method. This method uses a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the OR (50).

In this systematic review, we formally investigated the presence of publication bias using a series of publication bias regression and sensitivity plots (e.g., the Egger regression method and the trim and fill method). For the ongoing pregnancy rate, publication bias was found to be unlikely (Egger score = 0.24; 95% CI = -2.19-2.67, $P = .83$). Even so, using the trim and fill method to determine bias sensitivity revealed that one study (empty circle in Fig. 1B) may be imputed to bring symmetry to the funnel plot. The resulting meta-analysis outcome would still be significant: OR = 1.50 (95% CI = 1.36-1.65).

For the clinical pregnancy rate, publication bias was found to be unlikely (Egger score = 0.21; 95% CI = -1.12-1.54, $P = .74$). In addition, using the trim and fill method to determine bias sensitivity revealed that no studies need to be imputed to bring symmetry to the funnel plot. Therefore the resulting meta-analysis remains significant: OR = 1.50 (95% CI = 1.38-1.62).

TABLE 2

Review table of the primary outcome measures of the included studies, comparing ultrasound-guided ET with clinical touch ET.

Outcome measure	Comparison	No of studies	No. of cycles	Effect size*
Live-birth rate	All trials	2	615	1.78 (1.19 to 2.67)
	Properly randomized trials only	2	615	1.78 (1.19 to 2.67)
	Fresh, nondonor cycles only	2	615	1.78 (1.19 to 2.67)
	Oocyte donation cycles only	0	0	Not estimable
	Frozen embryo replacement cycles only	0	0	Not estimable
Ongoing pregnancy rate	All trials	10	3,967	1.51 (1.31 to 1.74)
	Properly randomized trials only	7	2,531	1.49 (1.25 to 1.78)
	Fresh, nondonor cycles only	8	3,050	1.55 (1.33 to 1.82)
	Oocyte donation cycles only	1	374	1.27 (0.84 to 1.90)
	Frozen embryo replacement cycles only	2	984	1.42 (1.04 to 1.93)
Clinical pregnancy rate	All trials	20	5,968	1.50 (1.34 to 1.67)
	Properly randomized trials only	8	2,731	1.46 (1.23 to 1.72)
	Fresh, nondonor cycles only	17	4,949	1.54 (1.36 to 1.74)
	Oocyte donation cycles only	1	374	1.22 (0.81 to 1.84)
	Frozen embryo replacement cycles only	3	1,225	1.25 (0.97 to 1.62)
Implantation rate	All trials	10	11,503	1.35 (1.22 to 1.50)
	Properly randomized trials only	5	5,270	1.47 (1.25 to 1.72)
	Fresh, nondonor cycles only	8	9,603	1.35 (1.21 to 1.51)
	Oocyte donation cycles only	0	0	Not estimable
	Frozen embryo replacement cycles only	2	2,197	1.42 (1.11 to 1.81)
Secondary outcomes	Multiple pregnancy rate	7	1,148	0.96 (0.72 to 1.27)
	Ectopic pregnancy rate	8	3,878	0.66 (0.30 to 1.45)
	Miscarriage rate	8	1,145	0.87 (0.61 to 1.26)
	Ease of transfer			
	Difficult embryo transfer	11	4,724	0.68 (0.58 to 0.81)
	Failure using the assigned catheter	6	3,324	0.20 (0.09 to 0.45)
	Instrumental assistance during transfer			
	All aspects	8	3,982	0.61 (0.50 to 0.74)
	Use of tenaculum	8	3,982	0.50 (0.39 to 0.64)
	Using stylette	5	2,768	0.94 (0.70 to 1.26)
	Using sounding	4	2,484	0.07 (0.02 to 0.32)
	Using dilatation	6	3,058	0.36 (0.10 to 1.24)
	Catheter tip			
Blood	6	2,613	0.53 (0.40 to 0.70)	
Mucus	2	900	0.33 (0.01 to 8.21)	
Retained embryos	7	3,002	0.41 (0.16 to 1.01)	

* Statistically significant.

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The possibility of publication bias opens up the door for questioning the results of any meta-analysis; therefore, further inspection and interpretation are needed to formulate definite conclusions. With regard to the 20 included trials, there was a general trend toward better results with ultrasound guidance, with only a limited number of studies demonstrating equivocal or better results with the clinical touch method. In addition, there was no statistical heterogeneity shown by either the scatter plot or the χ^2/I^2 tests, with regard to the primary outcomes. It may be assumed that studies with

equivocal results demonstrate that some clinicians have an excellent clinical sense, therefore nullifying any extra advantage provided by sonographic visualization.

Another important issue is the sample size of clinical trials and systematic reviews. It is theorized that some of the smaller trials did not have sufficient sample sizes to detect minor differences between the study groups. The largest included study ($N = 800$) had enough power to detect an 8% difference in clinical pregnancy rates (16). Our current

meta-analysis included 5,968 ET cycles and could detect an absolute difference of 3.3% with 80% power in a two-tailed analysis (assuming a clinical pregnancy rate of 30% with clinical touch alone and a significance level of .05). The absolute difference between ultrasound-guided and clinical touch ET was 7.7%, therefore validating our results. The number needed to treat to obtain one additional clinical pregnancy with use of ultrasound guidance is 13 (95% CI = 10–19).

The exact mechanism whereby ultrasound-guided ET improves pregnancy rates and embryo implantation remains unclear. Several theories have been proposed to identify the mechanisms whereby the transfer technique is optimized. These include confirming the position of the tip of the ET catheter within the uterine cavity, the site of embryo deposition, increasing the frequency of “easy” ETs, and avoiding endometrial indentation (36).

Nevertheless, some clinicians argue that the real benefit of ultrasound guidance lies in the ability to increase the clinical appreciation of the pelvic anatomy during transfer. They infer that ultrasound guidance, compared with the standard clinical touch alone, will not significantly increase the pregnancy rates when ET is performed by experienced professionals. Even so, this simple modification will allow for standardization of the transfer technique and therefore decrease any unexpected variation in pregnancy rates among different clinicians in the same center.

Whatever the underlying mechanism, the overall conclusion from this meticulous systematic review is that ultrasound-guided ET with use of 2-D–transabdominal ultrasound is significantly more effective than ET by clinical touch alone. It is believed that our overall analysis, and subgroup analyses, represents both a robust evaluation of the available evidence in the medical literature and also the best available evidence-based conclusions to support ultrasound guidance during ET.

The results of this systematic review demonstrate that ultrasound guidance during ET placement is a beneficial tool in optimizing the outcome of the ET procedure. This is in line with results of previously published clinical trials, systematic reviews (35, 36), and published guidelines (53). In addition, we have demonstrated that the beneficial effect is not limited only to patients with fresh but also those with frozen embryo replacement. It is also hoped that this evidence will be easily and quickly translated from the medical literature to everyday clinical practice.

Last, it is also important to note that until today, no study has reported any direct adverse effects of ultrasound-guided ET. Even so, one may argue that the main disadvantages of ultrasound-guided ETs are the need for more time, space, equipment, and trained ultrasound personnel. In addition, possible psychological stress may be caused in some patients who are forced to micturate after the transfer procedure, therefore disrupting the period of absolute bed rest. This issue can be managed easily through proper counseling before the

procedure on the amount of time needed for bed rest after ET, which is currently recommended as 20 minutes (53).

Also an additional cost to the transfer cycle may be associated with the preferred usage of echogenic catheters by some clinicians. The manufacturers of ET catheters have begun to market new echogenic versions of their standard catheters, which are sold for a 25% to 40% higher price tag than the original product, adding additional costs to the treatment cycle. Even so, it is of the utmost importance to note that even though echogenic catheters promise to be cost-effective by providing clinicians with more ultrasonographic visibility, easier transfers, and higher pregnancy rates than their competitor nonechogenic catheters, these points have not been proved in the literature, apart from more visibility. The pregnancy rates have been equivocal with the echogenic catheters. Therefore echogenicity currently should be left up to individual clinical preference and not standardized. Finally, it would be helpful for clinicians to perform in-house cost-effective analyses to determine the best combination of needed equipment, personnel, and catheter choice to provide the most efficient and cost-effective treatment options for patients.

In conclusion, according to the best available evidence in the medical literature today, the use of transabdominal ultrasound guidance to guide catheter placement during ET both is beneficial and should become the standard of care for all patients.

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REFERENCES

1. Edwards RG. Clinical approaches to increasing uterine receptivity during human implantation. *Hum Reprod* 1995;10(Suppl 2):60–6.
2. Mansour RT, Aboulghar MA. Optimizing the embryo transfer technique. *Hum Reprod* 2002;17:1149–53.
3. Lesny P, Killick SR, Tetlow RL, Robinson J, Maguiness SD. Embryo transfer—can we learn anything new from the observation of junctional zone contractions? *Hum Reprod* 1998;13:1540–6.
4. Abou-Setta AM, Al-Inany HG, Mansour RT, Serour GI, Aboulghar MA. Soft versus firm embryo transfer catheters for assisted reproduction: a systematic review and meta-analysis. *Hum Reprod* 2005;20:3114–21. Epub 2005 Jul 22.
5. Abou-Setta AM. Firm embryo transfer catheters for assisted reproduction: a systematic review and meta-analysis using direct and adjusted indirect comparisons. *Reprod Biomed Online* 2006;12:191–8.
6. Mansour R, Aboulghar M, Serour G. Dummy embryo transfer: a technique that minimizes the problems of embryo transfer and improves the pregnancy rate in human in vitro fertilization. *Fertil Steril* 1990;54:678–81.
7. Strickler RC, Christianson C, Crane JP, Curato A, Knight AB, Yang V. Ultrasound guidance for human embryo transfer. *Fertil Steril* 1985;43:54–61.
8. Leong M, Leung C, Tucker M, Wong C, Chan H. Ultrasound-assisted embryo transfer. *J In Vitro Fert Embryo Transf* 1986;3:383–5.
9. al-Shawaf T, Dave R, Harper J, Linehan D, Riley P, Craft I. Transfer of embryos into the uterus: how much do technical factors affect pregnancy rates? *J Assist Reprod Genet* 1993;10:31–6.

10. Blake K. Prospective randomised trial to evaluate the role of ultrasound during transcervical embryo transfer. (Unpublished.) National Research Register. Available from: URL: <http://www.nrr.nhs.uk/ViewDocument.asp?ID=N0013076690>.
11. de Camargo Martins AM, Baruffi RL, Mauri AL, Petersen C, Oliveira JB, Contart P, et al. Ultrasound guidance is not necessary during easy embryo transfers. *J Assist Reprod Genet* 2004;21:421–5.
12. Drakeley AJ, Lunt R, Aust T, Williamson P, Gazvani R, Sklavounos J, et al. A randomised trial of 2250 women having ultrasound guided embryo transfer. *Hum Reprod* 2006;21(Suppl 1):i82.
13. Garcia-Velasco JA, Isaza V, Martinez-Salazar J, Landazabal A, Requena A, Remohi J, et al. Transabdominal ultrasound-guided embryo transfer does not increase pregnancy rates in oocyte recipients. *Fertil Steril* 2002;78:534–9.
14. Matorras R, Urquijo E, Mendoza R, Corcostegui B, Exposito A, Rodriguez-Escudero FJ. Ultrasound-guided embryo transfer improves pregnancy rates and increases the frequency of easy transfers. *Hum Reprod* 2002;17:1762–6.
15. Prapas Y, Prapas N, Hatziparasidou A, Vanderzwalmen P, Nijs M, Prapa S, et al. Ultrasound-guided embryo transfer maximizes the IVF results on day 3 and day 4 embryo transfer but has no impact on day 5. *Hum Reprod* 2001;16:1904–8.
16. Tang OS, Ng EH, So WW, Ho PC. Ultrasound-guided embryo transfer: a prospective randomized controlled trial. *Hum Reprod* 2001;16:2310–5.
17. Weissman A, Farhi J, Steinfeld Z, Mutsafi R, Nahum H, Levran D. A prospective, randomized study of ultrasound-guided embryo transfer. *Fertil Steril* 2003;80(Suppl 3):S122.
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;327:557–60.
19. Garcia-Velasco JA, Martinez-Salazar J, Isaza V, Landazabal A, Requena A, Simón C. Does ultrasound guidance at embryo transfers improve pregnancy rates in oocyte recipients? *Fertil Steril* 2001;76(Suppl 1):S75–6.
20. Li R, Zhuang GL, Cai ZM, Wang H, Zhong K, Zhou WY. [Clinical analysis of ultrasound-guided embryo transfer after in-vitro fertilization]. *Zhonghua Fu Chan Ke Za Zhi* 2004;39:180–3.
21. Martins AMVC, Baruffi RLR, Mauri AL, Petersen C, Oliveira JBA, Contart P, et al. Ultrasound guidance for embryo transfer in patients previously identified by mock transfer as likely to have an easy transfer: a controlled trial. The 20th Annual Meeting of the European Society of Human Reproduction and Embryology. *Hum Reprod* 2004;19(Suppl 1):i73.
22. Abdelmassih VG, Abdelmassih ST, Nagy ZP, Abdelmassih R, Balmaceda J. The effect of ultrasound (US) guided embryo transfer (ET) and the choice of catheter on the outcome of IVF. *Fertil Steril* 2001;76(Suppl 1):S88–9.
23. Bar Hava I, Meltzer S, Rabinson J, Ayash I, Segal S, Tur Kaspas I. Ultrasound guided versus blind tactile embryo transfer: a prospective randomized study. *Hum Reprod* 2003;18(Suppl 1):xviii7.
24. Coroleu B, Barri PN, Carreras O, Martinez F, Veiga A, Balasch J. The usefulness of ultrasound guidance in frozen-thawed embryo transfer: a prospective randomized clinical trial. *Hum Reprod* 2002;17:2885–90.
25. Coroleu B, Carreras O, Veiga A, Martell A, Martinez F, Belil I, et al. Embryo transfer under ultrasound guidance improves pregnancy rates after in-vitro fertilization. *Hum Reprod* 2000;15:616–20.
26. Kan AK, Abdalla HI, Gafar AH, Nappi L, Ogunyemi BO, Thomas A, et al. Embryo transfer: ultrasound-guided versus clinical touch. *Hum Reprod* 1999;14:1259–61.
27. Kosmas IP, Janssens R, De Munck L, Al Turki HF, Tournaye H, Van Steirteghem AC, et al. Ultrasound guidance during embryo transfer does not offer any benefit in clinical outcome: a randomized controlled trial. *Hum Reprod* 2006;21(Suppl 1):i101.
28. Li R, Lu L, Hao G, Zhong K, Cai Z, Wang W. Abdominal ultrasound-guided embryo transfer improves clinical pregnancy rates after in vitro fertilization: experiences from 330 clinical investigations. *J Assist Reprod Genet* 2005;22:3–8.
29. Maldonado LG, Ajzen SA, Busato WC, Iaconelli A, Bibancos M, Borges E. Impact of previous hysterosonometry on embryo transfer. *Fertil Steril* 2005;84(Suppl 1):S364.
30. Marconi G, Young E, Vilela M, Bello A, Young E, Sueldo C. Prospective randomized comparison of an ultrasound-guided embryo transfer versus a blind catheter placement. *Fertil Steril* 2003;80(Suppl 3):S130.
31. Moraga-Sanchez MR, Saucedo-de la Llata E, Batiza-Resendiz V, Santos-Haliscak R, Galache-Vega P, Hernández-Ayup S, et al. Abstracts of the 20th Annual Meeting of the European Society of Human Reproduction and Embryology, Berlin, Germany. *Hum Reprod* 2004;19(Suppl 1):i127.
32. Prapas Y, Prapas N, Hatziparasidou A, Prapa S, Nijs M, Vanderzwalmen P, et al. The echoguide embryo transfer maximizes the IVF results. *Acta Eur Fertil* 1995;26:113–5.
33. Sallam HN, Agameya AF, Rahman AF, Ezzeldin F, Sallam AN. Ultrasound measurement of the uterocervical angle before embryo transfer: a prospective controlled study. *Hum Reprod* 2002;17:1767–72.
34. Wisanto A, Janssens R, Deschacht J, Camus M, Devroey P, Van Steirteghem AC. Performance of different embryo transfer catheters in a human in vitro fertilization program. *Fertil Steril* 1989;52:79–84.
35. Buckett WM. A meta-analysis of ultrasound-guided versus clinical touch embryo transfer. *Fertil Steril* 2003;80:1037–41.
36. Sallam HN, Sadek SS. Ultrasound-guided embryo transfer: a meta-analysis of randomized controlled trials. *Fertil Steril* 2003;80:1042–6.
37. Lu MC. Impact of “non-physician factors” on the “physician factor” of in vitro fertilization success: is it the broth, the cooks, or the statistics? *Fertil Steril* 1999;71:998–1000.
38. Goudas VT, Hammitt DG, Damario MA. Blood on the embryo transfer catheter is associated with decreased rates of embryo implantation and clinical pregnancy with the use of in vitro fertilization–embryo transfer. *Fertil Steril* 1998;70:878–82.
39. Ghazzawi IM, Al-Hasani S, Karaki R, Sousa S. Transfer technique and catheter choice influence the incidence of transcervical embryo expulsion and the outcome of IVF. *Hum Reprod* 1999;14:677–82.
40. Woolcott R, Stanger J. Ultrasound tracking of the movement of embryo-associated air bubbles on standing after transfer. *Hum Reprod* 1998;13:2107–9.
41. Waterstone J, Curson R, Parsons J. Embryo transfer to low uterine cavity. *Lancet* 1991;337:1413.
42. Yovich JL, Turner SR, Murphy AJ. Embryo transfer technique as a cause of ectopic pregnancies in in vitro fertilization. *Fertil Steril* 1985;44:318–21.
43. Friedler S, Lewin A, Schenker JG. Methodology of human embryo transfer following assisted reproduction. *J Assist Reprod Genet* 1993;10:393–404.
44. Al-Inany HG, Abou-Setta AM, Garzo G. ET catheters for assisted reproduction. *Cochrane Database Syst Rev* 2006;1:CD005636. DOI: 10.1002/14651858.CD005636.
45. Kojima K, Nomiya M, Kumamoto T, Matsumoto Y, Iwasaka T. Transvaginal ultrasound-guided embryo transfer improves pregnancy and implantation rates after IVF. *Hum Reprod* 2001;16:2578–82.
46. Baba K, Ishihara O, Hayashi N, Saitoh M, Taya J, Kinoshita K. Three-dimensional ultrasound in embryo transfer. *Ultrasound Obstet Gynecol* 2000;16:372–3.
47. Dickerson K, Min YL, Meinert CL. Factors influencing publication of research results. *JAMA* 1992;267:374–8.
48. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;337:867–72.
49. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.5 [updated May 2005]*. In: *The Cochrane Library, Issue 3, 2005*. Chichester, United Kingdom: John Wiley & Sons.
50. Egger M, Davy-Smith G, Schneider M, Minder CE. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
51. Deeks JJ, Higgins JPT, Altman DG, editors. *Analysing and presenting results*. In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions 4.2.5 [updated May 2005]*; Section 8. Available from: URL: <http://www.cochrane.org/resources/handbook/hbook.htm>. Accessed May 25, 2005.
52. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455–63.
53. National Institute for Clinical Excellence. *Fertility assessment and treatment for people with fertility problems*. London: RCOG Press, 2004:112.