Optimizing the embryo transfer technique
Abou-Setta, A.M.

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Chapter 9

What is the best site for embryo deposition? A systemic review and meta-analysis.

Ahmed M. Abou-Setta

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Abstract
The site of embryo replacement has been postulated as being important to the success of IVF/ICSI. In order to determine the best site for embryo deposition during embryo transfer, a meta-analysis of randomized trials comparing different uterine deposition sites was undertaken. Electronic (e.g. PubMed, EMBASE, Cochrane Library, LILACS) and hand searches were performed to locate trials. Outcomes measures were the live-birth (LBR), ongoing pregnancy (OPR), and clinical pregnancy rates (CPR). Assessments of the endometrial cavity length (ECL) and the distance from the fundus to the tip of the catheter (DTC) were utilized. Six studies were identified, of which three were excluded. Meta-analysis was conducted with the Mantel-Haenszel method, utilizing the fixed-effects model. The LBR and OPR showed an increasing trend when transfers were performed to the lower half of the uterine cavity. For the DTC, all rates were significantly higher for the ~20 mm versus ~10 mm distance from the uterine fundus, supporting the results of the ECL analysis. The results of this systematic review show that there is limited evidence of the superiority of lower cavity transfers (e.g. ~20 mm) compared with the traditional high cavity (e.g. ~10 mm) transfers. More well-designed and powered randomized trials are needed to confirm this conclusion.

Key words: embryo transfer, endometrial cavity length, IVF, meta-analysis, pregnancy rates
Introduction

Treatment of infertile couples through IVF has shown remarkable improvements since it was first described by Steptoe and Edwards (1). Since then, almost all aspects of the IVF procedure have been optimized in order to increase pregnancy rates through increased efficiency and effectiveness of the different aspects involved. Thus far, this is only partially true for the embryo transfer technique. Ever since it was first described, few modifications have been made to this inefficient procedure.

At present there is no standard, worldwide-accepted and evidence-based clinical protocol for the intrauterine transfer of embryos. In contrast to other aspects of the IVF procedure which have been more thoroughly addressed in the literature, most clinicians have relied on prior experience and personal preference when performing embryo transfer.

In addition, historically, little attention has been paid to the embryo transfer procedure. This fact is reflected by the dearth of scientific publications regarding embryo transfer compared with other aspects of IVF (e.g. ovulation induction), and also the reluctance of physicians to modify their own personal habits to encompass a more evidence-based approach.

Physicians, too, often underestimate the importance of the embryo transfer technique, being an apparently simple manoeuvre. Most inexperienced clinicians do not consider inserting a catheter through the uterine cervix and ejecting embryo-containing fluid to be a difficult task. This task may even be compared with the simple hysterosalpingography procedure done by most first year gynaecology residents. Nevertheless, it has been shown that the attitude of physicians towards the embryo transfer technique are changing for the better (2, 3).

Recently, the techniques and variables affecting the success of embryo transfer have attracted more attention. Today, in light of global trends such as single embryo transfer (SET), more emphasis has been placed on optimizing and standardizing the embryo transfer protocol than ever before (2, 3).

The pregnancy rate after embryo transfer is dependent upon multiple factors, including embryo quality, endometrial receptivity and the technique of the embryo transfer itself (4). In recent years, more emphasis has been placed on optimizing and standardizing the embryo
transfer protocol. Factors such as catheter choice (5, 6), ease of the procedure in order to prevent endocervical and endometrial damage (7, 8), ultrasound-guidance (9-11), flushing the endometrium (12) and dummy embryo transfer (13) have proven to affect clinical outcomes. In order to ascertain the importance of each step involved in the embryo transfer procedure, individual factors must be evaluated independently. Consequently, any modification in the standard protocol that will improve the outcomes is of great value.

The influence of the depth of embryo replacement into the uterine cavity has been postulated as being one of the most important factors to the success of an IVF treatment cycle (14). Traditionally, most IVF programmes have relied on the clinician’s ‘clinical touch’ for the placing of the transfer catheter within the uterine cavity at a point ‘near’ the fundus (3, 15). Today this procedure has been modified to utilize ultrasound guidance to direct the placement of the catheter tip, allowing for more accurate placement (11).

At present, the best site of embryo deposition is still not clear and remains highly debated. This debate has been fuelled by conflicting results from published clinical trials. Therefore, in light of this controversy and the need to clearly identify the best site for catheter placement and embryo deposition during embryo transfer, it was decided to systematically locate, analyse and review the best available current evidence on the site of embryo deposition.
Materials and methods

Criteria for considering studies for this review
All published, unpublished and ongoing randomized trials reporting data that compared outcomes for women undergoing embryo transfer through the cervical route following IVF, or intracytoplasmic sperm injection (ICSI), and randomized according to distance to the tip of the catheter (DTC) and the uterine fundus or endometrial cavity length (ECL) were sought, in all languages.

Types of outcome measures
The outcome measures for this systematic review were the live-birth (LBR), ongoing pregnancy (OPR), and clinical pregnancy (CPR) rates.

Search strategy for identification of studies
Meticulous computerized searches were conducted using MEDLINE (1966 - July 2006), EMBASE (1980 – July 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library Issue 3, 2006, the National Research Register (NRR), and the Trial Register of Controlled Trials (www.controlled-trials.com) and the Latin American and Caribbean Health Sciences Literature database (LILACS). The following Medical Subject Headings (MeSH) and text words were used: embryo transfer, embryo transfer technique, ultrasound, ultrasound-guided embryo transfer, endometrial cavity length, embryo implantation, and randomized controlled trial(s).
Furthermore, the reference lists of all known primary studies, review articles, citation lists of relevant publications, abstracts of major scientific meetings (e.g. ESHRE and ASRM) 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 organisations.

Methods of review
A standardized data extraction form was developed and piloted for consistency and completeness. Trials were considered for inclusion, and trial data extracted. Data management and statistical analyses were conducted using the Review Manager (RevMan) 4.3 and Power and Sample Size Calculations (PS) 2.1.30 statistical software packages.
Individual outcome data were included in the analysis if they met the pre-stated criteria. Where possible, data was extracted to allow for an intention-to-treat analysis; defined as including in the denominator all randomized cycles. If data from the trial reports was insufficient or missing, the investigators of individual trials were contacted via e-mail for additional information, in order to perform analyses on an intention-to-treat basis.

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Heterogeneity of the included studies was determined by visual inspection of the outcome tables and by using the $I^2$-test for heterogeneity. In addition, the $I^2$ test was used to try to quantify any apparent inconsistency. The $I^2$ test is a statistical measure used to quantify heterogeneity. It describes the percentage of the variability within effect estimates that is due to heterogeneity rather than sampling error (chance) (16). An $I^2$ value greater than 50% may be considered to represent substantial heterogeneity.

**Comparison methods**

For the meta-analysis, the number of participants experiencing the event in each group of the trial was recorded. Two comparative methods were used for evaluation: the direct (head-to-head) and the adjusted indirect comparison methods. For the direct comparisons, comparison of the result of group B with the result of group C within a randomized controlled trial gave an estimate of the efficacy of intervention B versus C. Direct comparison was undertaken using the Mantel-Haenszel method utilizing the fixed-effects model, and the odds ratio and 95% confidence interval (CI) evaluated.

If direct comparison was not possible due to the lack of available trials comparing group B with group C, then adjusted indirect comparison was performed using the method described by Bucher et al. (17, 18). The indirect comparison of intervention B and C was adjusted by the results of their direct comparisons with a common intervention A.

In brief, given two estimated effects $\theta_{AB}$ and $\theta_{AC}$ for comparisons of group A versus group B (AvB) and group A versus group C (AvC), respectively, then the effect for the comparison of group B versus C (BvC) is estimated as follows: $\theta_{BC} = \theta_{AB} - \theta_{AC}$, and its variance is $\text{var}(\theta_{BC}) = \text{var}(\theta_{AB}) + \text{var}(\theta_{AC})$. A 95% confidence interval for $\theta_{BC}$ is
obtained as $\theta_{BC} \pm 1.96 \sqrt{\text{var}(\theta_{BC})}$. The estimates of effect, denotes $\theta$, relate to scale on which the data would be analyzed; in this case being the log odds ratio.

**Search results**
A total of six prospective randomized controlled trials were identified (four full-text manuscripts and two conference abstracts) (Figure 1). Subsequently, three trials were excluded due to duplicate publication [e.g. publication as a conference abstract and full-text manuscript (19, 20), or double publication as full-text manuscripts (21)]. The remaining three trials were included, and the methodological quality of each trial assessed. Finally, data was extracted to allow for an intention-to-treat analysis.

**Description of included studies**
Nazari et al. (22) conducted a randomized controlled trial including 1008 women undergoing 1590 embryo transfer cycles. All cycles were performed using the clinical touch method of catheter placement. In order to determine the best site for embryo deposition, patients were randomly allocated into one of two groups: embryo placement $<5$ mm (group I), and embryo placement $>15$ mm (group II) from the uterine fundus. The length of the uterine cavity was determined during a mock embryo transfer. For the purpose of this systematic review, groups I and II will be denoted as N-I and N-II respectively. The cycles were randomly allocated using a 2:1 ratio: N-I ($n = 660$ cycles) and N-II ($n = 930$ cycles). The transfer procedures were performed by five physicians (two allocated to N-I and three allocated to N-II), and both fresh and frozen embryo replacement (FER) cycles were included in the analysis. Only one catheter type was used for all transfers (Short Frydman Embryo Transfer Set; Laboratoire CCD, Paris, France). Physicians were allocated to the two groups by randomly picking numbered envelopes. Clinical pregnancy rates were defined as the presence of a gestational intrauterine sac on ultrasound.

Coroleu et al. (23) conducted a randomized controlled trial including 180 women undergoing 180 embryo transfer cycles. All cycles were performed using ultrasound guidance to guide catheter placement. In order to determine the best site for embryo deposition, patients were randomly allocated into one of three groups, using a computer-
generated randomization table: embryo placement 10 ± 1.5 mm (group I), embryo placement 15 ± 1.5 mm (group II), and embryo placement 20 ± 1.5 mm (group III) from the uterine fundus. The site of deposition was determined during the actual embryo transfer by the use of ultrasonography. For the purpose of this systematic review, groups I, II and III will be denoted as C-I, C-II and C-III respectively. The cycles were randomly allocated using a 1:1:1 ratio: C-I (n = 61 cycles), C-II (n = 59 cycles), and C-III (n = 60 cycles). The transfer procedures were done by one physician, with the same catheter type used in all transfers (Edwards-Wallace Embryo Replacement Catheter; Smiths Medical International Ltd., Kent, UK), and only fresh, non-donor cycles were included in the analysis. Clinical pregnancy rates were defined as the presence of a gestational intrauterine sac on ultrasound.

Franco et al. (24) conducted a prospective, randomized controlled trial including 360 women undergoing 400 embryo transfer cycles. All cycles were performed using ultrasound guidance to guide catheter placement. In order to determine the best site for embryo deposition, patients were randomly allocated into one of two groups, by drawing lots from a random-number table, depending on the site of embryo deposition. In all cases the endometrial cavity length (ECL) was measured immediately before transfer. In group I, embryos were deposited in the upper half of the endometrial cavity (e.g. <50% ECL) and in group II embryos were deposited in the lower half of the endometrial cavity (e.g. ≥50% ECL). The site of deposition was determined during the actual embryo transfer by the use of ultrasonography. For the purpose of this systematic review, groups I and II will be denoted as F-I and F-II respectively. The cycles were randomly allocated using a 1:1 ratio: F-I (n = 200 cycles) and C-II (n = 200 cycles). The transfer procedures were carried out by the same physician, with the same catheter type used in all transfers (Frydman Embryo Classic Catheter 4.5), and only fresh, non-donor cycles were included in the analysis. Clinical pregnancy rates were defined as the presence of a gestational intrauterine sac with cardiac activity on ultrasound. Ongoing pregnancy rates were defined as a viable fetus on ultrasound at 12 weeks.
Results
Table 1 provides an assessment of the quality of the included trials. An a priori sample size calculation, to determine the adequate sample size needed, was performed by only one study (22). The method of randomization and randomization concealment was clear and adequate in two studies (23, 24). In addition, all studies used an intention-to-treat analysis when analysing their data. Finally, possible confounders were obvious in the study by Nazari et al. (22). They included the use of both fresh and frozen embryo transfer cycles and multiple (n = 5) physicians performing the embryo transfer. In the original publications, none of the included studies presented the live-birth rate, but two studies (23, 24) presented the ongoing pregnancy rate. The missing ongoing pregnancy and live-birth rates for all the studies were provided following personal contact with the respective authors.
Table 2 shows the intended distance of embryo disposition from the uterine fundus and the actual average distance of embryo deposition for the included studies. It is noticeable that even though physicians intended to deposit the embryos at an exact distance from the uterine fundus, factors including endometrial wave contractions and hydraulic force, served to move the embryos up or down a few millimetres from the intended site. Table 3 shows the numbers of clinical pregnancies, ongoing pregnancies and live births in the original studies. Two analyses were performed in an attempt to locate the best site of embryo deposition. The first was performed by dividing the average-sized uterus into two parts (i.e. upper half and lower half) according to the endometrial cavity length (ECL). In a second series of analyses, the position of the catheter tip was examined with regard to the distance from the fundus to the tip of the catheter (DTC). Finally, a subgroup analysis was performed for studies that used ultrasound-guidance during embryo transfer, as this is considered the proper method of determining the exact site of embryo deposition.

Assessment of endometrial cavity length
The average uterine endometrial cavity length (ECL) is considered to be ~30 mm (21). Therefore, the individual study groups were allocated to transfer to the upper half (i.e. ECL <50% or <15 mm) or the lower half (i.e. ECL >50% or >15 mm) of the uterus. This analysis was performed twice using two different algorithms (Table 4). The site of embryo
Deposition was not significantly different with regard to the live-birth, ongoing pregnancy, and clinical pregnancy rates between the two groups in either analysis. Even so, it should be noted that there was an apparent trend with regard to transfers to the lower half of the uterine cavity.

Assessment of distance from the fundus to the tip of the catheter (DTC)
For the purpose of these analyses, the uterine cavity was arbitrarily divided into five regions as follows: DTC-I = <7.25 mm, DTC-II = 10 ± 2.5 mm, DTC-III = 15 ± 2.5 mm, DTC-IV = 20 ± 2.5 mm and DTC-V = >22.5 mm (Table 5). It is important to note that an additional section (i.e. DTC-III/DTC-IV) was added to allow for a more appropriate analysis of the available data. Furthermore, each section was compared with the other sections and the results are presented in Table 6. In this series, only the pooled analysis for live-birth, ongoing pregnancy and clinical pregnancy rates were significantly different for the analyses DTC-II (e.g. 10 ± 2.5 mm) versus DTC-IV (e.g. 20 ± 2.5 mm) (for ongoing pregnancy rates OR = 0.43, 95% CI = 0.20-0.89 and for clinical pregnancy rates OR = 0.43, 95% CI = 0.21-0.90). In addition, the analysis DTC-I versus DTC-III/IV showed significance with regard to the live-birth (OR = 0.70, 95% CI = 0.51-0.98) and ongoing pregnancy rates (OR = 0.71, 95% CI = 0.52-0.98), but this analysis was built on data from only one trial. The other analyses were not significantly different.

Subgroup analysis
In the analyses of the subgroups of studies that used ultrasound-guided embryo transfer, there were no differences in the clinical pregnancy, ongoing pregnancy or live births in the two ECL assessments, therefore denoting no significance between embryo deposition in the upper or lower halves of the uterine cavity. As for the DTC assessments, only the DTC-II versus DTC-IV analyses showed statistical significance with respect to the clinical pregnancy (OR = 0.43; 95% CI = 0.21-0.90), ongoing pregnancy (OR = 0.43; 95% CI = 0.20-0.89) and live-birth (OR = 0.42; 95% CI = 0.20-0.89) rates. It is important to note that this result was generated from only one included study (22).
Discussion

Embryo transfer is the final stage of the IVF cycle. It is also the instance where clinical manipulations can directly alter the outcome of the IVF cycle, and has shown marked variability among different IVF programmes, and also among physicians within in the same programme (25, 26).

Although most patients who undergo assisted reproduction, via IVF or ICSI, will reach the embryo transfer 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 should be to place embryos meticulously and accurately within the uterus, in order to allow for proper implantation and fetal development (14, 27).

The site of embryo placement in the uterine cavity has been suggested to directly influence the embryo implantation rates. Nevertheless, this clinical issue is not clearly addressed in the literature, with some authors recommending the tip of the embryo transfer catheter be placed ~10 mm below the fundal endometrial surface (28, 29) or close to the uterine fundus (27, 30), and others suggesting that improved results may be obtained when the embryos are placed at lower levels in the uterine cavity (7, 14, 22, 31-36). Finally, some authors postulate that the site of embryo transfer is of no importance, since it does not influence implantation, as long as embryos are placed in the upper half of the cavity (22, 37, 38).

Ironically, the site of transfer has also been related to poor pregnancy outcomes. Transferring embryos within 1 cm of the uterine endometrial fundus has been criticized as being associated with a higher than normal tubal ectopic pregnancy rate (22, 39). At the same time, low implantations have been shown to have a higher rate of spontaneous abortion, and cervical ectopic pregnancies (27, 37).

Another important factor is the use of ultrasound guidance in order to accurately place the tip of the embryo transfer catheter at the required site of embryo deposition. In addition to the accuracy provided by ultrasound visualization of the uterus, ultrasound-guided embryo transfer has been shown to improve the clinical pregnancy rate (9, 10) and live-birth rates (11) when compared with the traditional clinical touch method. Even so, this has been challenged by a recent large randomized trial that demonstrated similar clinical pregnancy and live-birth rates between the two methods (40). Nonetheless, there is no
disagreement of the fact that only with ultrasound guidance can the clinician confidently determine the site of deposition.

Two of the included studies (23, 24) utilized ultrasound guidance to determine the exact site of embryo deposition, while one study (22) used the traditional clinical touch method. The results of the subgroup analyses of only the studies using ultrasound guided embryo transfer did not differ from the results of the original analyses.

More importantly, the importance of the site of embryo deposition revolves around locating the best site for optimum embryo implantation in the human uterus. In a prospective study, it was documented that following embryo transfer, approximately 80% of embryos implant in areas to which they are transferred initially and approximately 20% implant in other areas (41).

Furthermore, using three-dimensional transvaginal ultrasound, Minami et al. (42) determined that the upper region of the uterine cavity contained the majority of early gestational sacs in an unselected population of pregnant women. Moreover, the miscarriage rate was significantly lower when the early sac was found in the upper region than in the middle and lower regions.

In another recent study, Cavagna et al. (43) studied 63 pregnancies following embryo transfer to the middle point of the endometrial cavity. This study documented that in singleton pregnancies, 66.0% of the gestational sacs were detected in the upper region, 29.8% in the middle region and 4.2% in the lower region. In multiple pregnancies, the rates were 45.5, 51.5 and 3.0% respectively. These results demonstrate that even when embryos are transferred to the central area of the uterine cavity, there is still a high chance of embryo implantation in the upper region.

Since systematic reviews and meta-analysis of randomized controlled trials have been proven to provide the highest level of evidence in the hierarchy of medical knowledge, it was decided to test the soundness of these theories. During this systematic review, both direct and adjusted indirect analyses were utilized. Since it is well accepted that well designed prospective, randomized, controlled trials provide the most valid evidence of relative efficacy of competing interventions, they are utilized first and foremost in evaluations. Nevertheless, many competing interventions have not been compared directly (head-to-head) in randomized trials. Because of the lack of direct evidence, indirect
comparisons have been recommended and used for evaluating the efficacy of alternative interventions (44).
Still, it may be argued that this review might not have sufficient sample sizes to detect minor differences between study groups. Study power and adequate sample sizes help to prevent the occurrence of type II errors. This current meta-analysis included 2570 embryo transfer cycles. With this large sample size, the ECL assessments could detect a 6% difference with 80% power in a two-tailed analysis (assuming a clinical pregnancy rate of 30% and a significance level of 0.05). Even so, since the DTC analyses were divided into more groups, ranging from 59 to 1189 cycles, there was evident heterogeneity in the examined sample sizes.

The results of this systematic review and meta-analysis show that (i) pregnancy rates are similar when the upper and lower halves of the endometrial cavity are compared, and (ii) mid-cavity transfer (e.g. ~20 mm) is superior to the traditional high transfer (e.g. ~10 mm). Even so, it is important to note that due to the sample size, firm conclusions cannot be made.

Moreover, it is of the utmost importance to note that there was clinical heterogeneity between the included studies. Therefore a series of meta-regression analyses were utilized to compare all aspects of embryo site deposition. Finally, even though every effort was used to locate trials in the medical literature, the final sample sizes in some of the calculations (e.g. DTC) tended to suggest a lack of statistical power, which brings in the possibility of type II errors. This will only be offset by the publication of more well designed and powered randomized controlled trials.

In conclusion, the results of this systematic review demonstrate that live-birth, ongoing pregnancy and clinical pregnancy rates may be influenced by the site of the embryo deposition. With the available evidence at hand, it may be recommended to position the tip of the catheter in the middle area of the endometrial cavity rather than at the currently recommended ~10 mm from the uterine fundus. Even so, due to the heterogeneity of the included studies and in some cases, the relatively small sample sizes, there is only limited evidence to support the proper site of embryo deposition. More well designed, and powered randomized controlled trials comparing the standard ~10 mm distance and the new suggested ~20 mm distance are needed to support the results of this systematic review. In addition, studies are needed to
address surrogate outcomes such as the effect of embryo deposition site on the rate of ectopic and spontaneous miscarriage.
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Figure 1. QUOROM statement flow diagram.

Potentially relevant RCTs Identified and screened for retrieval (n=6)

RCTs excluded, duplicate publication (n=3)

RCTs retrieved for more detailed evaluation (n=3)

RCTs withdrawn (n=0)

Potentially appropriate RCTs to be included in the meta-analysis (n=3)

RCTs withdrawn (n=0)

RCTs included in meta-analysis (n=3)

RCTs withdrawn (n=0)

RCTs with usable information, by outcome (n=3)

RCT = randomized controlled trials.
TABLE 1. Review table of the study quality of the included trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>A-priori sample size calculation</th>
<th>Method of Randomization</th>
<th>Method of Randomization Concealment</th>
<th>Intention-to-treat</th>
<th>Follow-up</th>
<th>Possible confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nazari et al. (22)</strong></td>
<td>Not performed</td>
<td>Physicians randomly picking numbered envelopes</td>
<td>Not performed</td>
<td>ITT</td>
<td>LBR</td>
<td>Multiple physicians, FET included</td>
</tr>
<tr>
<td><strong>Coroleu et al. (23)</strong></td>
<td>Not performed</td>
<td>Computer-generated randomization table</td>
<td>Tele-randomization</td>
<td>ITT</td>
<td>OPR</td>
<td>None evident</td>
</tr>
<tr>
<td><strong>Franco et al. (24)</strong></td>
<td>Performed</td>
<td>Random-number table</td>
<td>Drawing lots at time of embryo transfer</td>
<td>ITT</td>
<td>OPR</td>
<td>None evident</td>
</tr>
</tbody>
</table>

ITT = Intention to treat analysis performed; FET = Frozen-thawed embryo replacement cycles.
TABLE 2. Review table of the site of expected and actual distance of embryo deposition from the uterine fundus as reported in the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Site of Embryo Deposition</th>
<th>A priori transfer distance from Fundus</th>
<th>Actual transfer distance from Fundus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nazari et al. (22)</strong></td>
<td>N-I</td>
<td>&lt;5 mm</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N-II</td>
<td>&gt;15 mm</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Coroleu et al. (23)</strong></td>
<td>C-I</td>
<td>10 ± 1.5 mm</td>
<td>10.2 ± 0.9 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-II</td>
<td>15 ± 1.5 mm</td>
<td>14.6 ± 0.7 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-III</td>
<td>20 ± 1.5 mm</td>
<td>19.3 ± 0.8 mm</td>
<td></td>
</tr>
<tr>
<td><strong>Franco et al. (24)</strong></td>
<td>F-I</td>
<td>&lt;50 ECL</td>
<td>13.3 ± 1.6 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F-II</td>
<td>&gt;50% ECL</td>
<td>18.3 ± 3.2 mm</td>
<td></td>
</tr>
</tbody>
</table>

N-I, II = Group I, II in Nazari et al. (22), respectively. C-I, II, III = Group I, II and III in Coroleu et al. (23), respectively. F-I, II = Group I, II in Franco et al. (24), respectively. ECL = endometrial cavity length. NA = Not available.
### TABLE 3. Review table of the clinical pregnancy and live-birth rates as reported in the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Group</th>
<th>Number of embryo transfers</th>
<th>Number of Clinical Pregnancies (%)</th>
<th>Number of Ongoing Pregnancies (%)</th>
<th>Number of Live Births (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nazari et al. (22)</td>
<td>N-I</td>
<td>660</td>
<td>82 (12.42%)</td>
<td>63 (9.55%)</td>
<td>61 (9.24%)</td>
</tr>
<tr>
<td></td>
<td>N-II</td>
<td>930</td>
<td>132 (14.19%)</td>
<td>120 (12.90%)</td>
<td>118 (12.69%)</td>
</tr>
<tr>
<td>Coroleu et al. (23)</td>
<td>C-I</td>
<td>61</td>
<td>24 (39.34%)</td>
<td>20 (32.79%)</td>
<td>19 (31.15%)</td>
</tr>
<tr>
<td></td>
<td>C-II</td>
<td>59</td>
<td>29 (49.15%)</td>
<td>26 (44.07%)</td>
<td>25 (42.37%)</td>
</tr>
<tr>
<td></td>
<td>C-III</td>
<td>60</td>
<td>36 (60.00%)</td>
<td>32 (53.33%)</td>
<td>31 (51.67%)</td>
</tr>
<tr>
<td>Franco et al. (24)</td>
<td>F-I</td>
<td>200</td>
<td>70 (35.00%)</td>
<td>58 (29.00%)</td>
<td>58 (29.00%)</td>
</tr>
<tr>
<td></td>
<td>F-II</td>
<td>200</td>
<td>59 (29.50%)</td>
<td>50 (25.00%)</td>
<td>50 (25.00%)</td>
</tr>
</tbody>
</table>

N-I, II = Group I, II in Nazari et al. (22), respectively. C-I, II, III = Group I, II and III in Coroleu et al. (23), respectively. F-I, II = Group I, II in Franco et al. (24), respectively.
TABLE 4. Distribution of groups according to the endometrial cavity length (ECL).

<table>
<thead>
<tr>
<th>Study</th>
<th>ECL-I (&lt;15 mm)</th>
<th>ECL-II (≥15 mm)</th>
<th>LBR</th>
<th>OPR</th>
<th>CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nazari et al. (22)</td>
<td>N-I</td>
<td>N-II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Coroleu et al. (23) | C-I            | C-II/ C-III     | OR = 0.79  
95%CI = 0.62 to 1.01 | OR = 0.80  
95%CI = 0.63 to 1.01 | OR = 0.91  
95%CI = 0.72 to 1.14 |
| Franco et al. (24)  | F-I            | F-II            |     |     |      |
| **Analysis II**     |                |                 |     |     |      |
| Nazari et al. (22)  | N-I            | N-II            |     |     |      |
| Coroleu et al. (23) | C-I/ C-II      | C-III           | OR = 0.80  
95%CI = 0.63 to 1.01 | OR = 0.80  
95%CI = 0.63 to 1.01 | OR = 0.90  
95%CI = 0.72 to 1.13 |
| Franco et al. (24)  | F-I            | F-II            |     |     |      |

N-I, II = Group I, II in Nazari et al. (22), respectively. C-I, II, III = Group I, II and III in Coroleu et al. (23), respectively. F-I, II = Group I, II in Franco et al. (24), respectively. O.R = odds ratio; CI = confidence interval. CPR = clinical pregnancy rate; LBR = live birth rate; OPR = ongoing pregnancy rate.
TABLE 5. Distribution of groups according to the distance from the fundus to the tip of the catheter (DTC).

<table>
<thead>
<tr>
<th>Study</th>
<th>DTC-I (&lt;7.25 mm)</th>
<th>DTC-II (10 ± 2.5 mm)</th>
<th>DTC-III (15 ± 2.5 mm)</th>
<th>DTC-IV (20 ± 2.5 mm)</th>
<th>DTC-V (&gt;22.5 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nazari et al. (22)</strong></td>
<td>N-I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coroleu et al. (23)</strong></td>
<td></td>
<td>C-I</td>
<td>C-II</td>
<td>C-III</td>
<td></td>
</tr>
<tr>
<td><strong>Franco et al. (24)</strong></td>
<td></td>
<td>F-I</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N-I, II = Group I, II in Nazari et al. (22), respectively. C-I, II, III = Group I, II and III in Coroleu et al. (23), respectively. F-I, II = Group I, II in Franco et al. (24), respectively.
TABLE 6. Review table of the results of direct and adjusted indirect meta-analysis according to the distance from the fundus to the catheter tip (DTC).

(A) Live-birth rate

<table>
<thead>
<tr>
<th></th>
<th>DTC-II</th>
<th>DTC-III</th>
<th>DTC-IV</th>
<th>DTC-III/ DTC-IV</th>
</tr>
</thead>
</table>
| DTC-I  | OR = 0.76*  
         | 95%CI = 0.47 to 1.23* | NA     | NA              | OR = 0.70  
         |                           |         | 95%CI = 0.51 to 0.97 |
| DTC-II | OR = 0.62  
         | 95%CI = 0.29 to 1.30 | OR = 0.42  
         | 95%CI = 0.20 to 0.89 | OR = 0.92  
         | 95%CI = 0.64 to 1.32 |
| DTC-III| OR = 0.69  
         | 95%CI = 0.33 to 1.42 | NA     | NA              |
| DTC-IV | NA     | NA      | NA     | NA              |

DTC-I = <7.25 mm; DTC-II = 10 ± 2.5 mm; DTC-III = 15 ± 2.5 mm; DTC-IV = 20 ± 2.5 mm; O.R = odds ratio; CI = confidence interval; * adjusted indirect analysis; NA = not applicable.
(B) Ongoing pregnancy rate

<table>
<thead>
<tr>
<th></th>
<th><strong>DTC-II</strong></th>
<th><strong>DTC-III</strong></th>
<th><strong>DTC-IV</strong></th>
<th><strong>DTC-III/ DTC-IV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTC-I</strong></td>
<td>OR = 0.77* 95%CI = 0.48 to 1.25*</td>
<td>NA</td>
<td>NA</td>
<td>OR = 0.71 95%CI = 0.52 to 0.98</td>
</tr>
<tr>
<td><strong>DTC-II</strong></td>
<td></td>
<td>OR = 0.62 95%CI = 0.29 to 1.30</td>
<td>OR = 0.43 95%CI = 0.20 to 0.89</td>
<td>OR = 0.92 95%CI = 0.64 to 1.32</td>
</tr>
<tr>
<td><strong>DTC-III</strong></td>
<td></td>
<td></td>
<td>OR = 0.69 95%CI = 0.33 to 1.42</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DTC-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

DTC-I = <7.25 mm; DTC-II = 10 ± 2.5 mm; DTC-III = 15 ± 2.5 mm; DTC-IV = 20 ± 2.5 mm; O.R = odds ratio; CI = confidence interval; * adjusted indirect analysis; NA = not applicable.
(C) Clinical pregnancy rate

<table>
<thead>
<tr>
<th></th>
<th><strong>DTC-II</strong></th>
<th><strong>DTC-III</strong></th>
<th><strong>DTC-IV</strong></th>
<th><strong>DTC-III/ DTC-IV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTC-I</strong></td>
<td>OR = 0.88* 95%CI = 0.57 to 1.36*</td>
<td>NA</td>
<td>NA</td>
<td>OR = 0.86 95%CI = 0.64 to 1.15</td>
</tr>
<tr>
<td><strong>DTC-II</strong></td>
<td></td>
<td>OR = 0.67 95%CI = 0.33 to 1.38</td>
<td>OR = 0.43 95%CI = 0.21 to 0.90</td>
<td>OR = 0.98 95%CI = 0.69 to 1.38</td>
</tr>
<tr>
<td><strong>DTC-III</strong></td>
<td></td>
<td></td>
<td>OR = 0.64 95%CI = 0.31 to 1.33</td>
<td>NA</td>
</tr>
<tr>
<td><strong>DTC-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

DTC-I = <7.25 mm; DTC-II = 10 ± 2.5 mm; DTC-III = 15 ± 2.5 mm; DTC-IV = 20 ± 2.5 mm; O.R = odds ratio; CI = confidence interval; * adjusted indirect analysis; NA = not applicable.