

# The depth of embryo placement into the uterine cavity in IVF/ICSI cycles

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## Summary

**Purpose:** The purpose of the study was to analyze the depth of embryo placement in the uterine cavity. **Materials and Methods:** This paper provides a review of published literature through searches of PubMed and MEDLINE from 2004 to 2015 to identify relevant studies that compared outcomes, mainly implantation, and pregnancy rates for women undergoing embryo transfer (ET) through the cervix following in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI) cycles assessing the distance of where embryos were placed. A meta-analysis, three randomized controlled trials, and several retrospective and prospective studies were reviewed. **Results:** Most of the reviewed studies indicated that the embryo should be positioned at the tip of catheter in the middle area in regards of endometrial cavity around 10 to 20 mm away from fundus. Lower pregnancy rates have been also evaluated by the findings. **Conclusion:** It has been concluded that the site of embryo deposition usually affect the pregnancy rates and implantation.

**Key words:** Embryo; Fertilization; Pregnancy; Uterine cavity; Deposition.

## Introduction

Embryo transfer (ET) remains an important step for both physicians and the patients; similarly, the technique for accomplishing this process is also crucial [1]. Meldrum was among the first authors to publish an article on the importance of meticulous ET technique and its essence on in vitro fertilization (IVF) success [2]. Various factors affecting IVF success rate have been described in literature such as the type of catheter, the operator's skill, the amount of loaded medium, the presence of mucus or blood in or around the catheter, and difficulty in entering the uterine cavity [3-5]. Embryos are commonly transferred through the transcervical route, with the catheter being inserted either blindly by clinical touch or guided by ultrasound. Cochrane review has confirmed higher clinical pregnancy rate (CPR) and delivery rate when the ET was performed under US guidance compared with the clinical touch; however, they failed to show a difference between ultrasound-guided embryo transfer and clinical touch for the outcome of live birth [6]. The site of the uterine cavity where embryos are placed has also been considered as an important variable [7-12]. In the late 80s and the early 90s, published studies have suggested that embryos placed away from the fundus enhance pregnancy rates [2, 13, 14] and reduce the incidence of ectopic pregnancy after ET [15, 16].

## Materials and Methods

Qualitative research approach was used by this research study for the purpose of collecting data in regards of the same. Along with qualitative approach, systematic review and meta-analysis was also performed in order to assess the relevant outcomes. MEDLINE, ProQuest, ScienceDirect, Cochrane, and other databases have been searched for collecting research studies. The inclusion criteria for the selection of studies were successfully published in journals, available in different libraries, and published after the year 2005. All of the studies, which were found to be eligible, relevant, authentic, or strong resource during scrutiny process, were excluded from the study.

Systematic review and meta-analysis approach was used in order to analyze data effectively. The data analysis processes was also carried out in complete confidentiality and privacy. The approach of systematic review was widely supported by different studies as it was used by different published articles. It is because of systematic review and meta-analysis that a study can easily gather diverse range of data in a shorter sample.

The selected studies have compared outcomes, mainly related to implantation and pregnancy rates among women, who were undergoing ET through the cervix following IVF or intracytoplasmic sperm injection (ICSI) cycles assessing the distance of where embryos were placed. A meta-analysis, three randomized controlled trials, and several retrospective and prospective studies were reviewed. The distances described were either distance to the tip of the catheter (DTC) and the uterine fundus or endometrial cavity length (ECL). The definition in literature for the average uterine ECL was around 30 mm.

## Results

Coroleu *et al.* [7] analyzed 180 patients who had guided ET. The patients were divided into three groups according to the distance between the uterine fundus and the site of embryo placement: group 1,  $10 \pm 1.5$  mm; group 2,  $15 \pm 1.5$  mm, and group 3,  $20 \pm 1.5$  mm. Groups 2 and 3 had the best implantation and pregnancy rates [17].

Frankfurter *et al.* [10] prospectively analyzed 666 patients who underwent fresh IVF cycles performed in 2001. There were 393 fundal and 273 lower to middle uterine segment ETs performed. Pregnancy rate (PR), implantation, and birth rates were significantly higher after a middle to lower uterine segment ET compared with fundal ET (39.6% vs. 31.2%, 21% vs. 14%, and 34.1% vs. 26.2%, respectively). When the distance of the embryo placement was away for the uterine fundus relative to the length of the endometrial cavity, the pregnancy rates were higher [10]. Other authors have reported similar findings, where pregnancy rates were higher when the embryos were placed disposed at a lower level in the uterine cavity [17–20]. A plethora of studies on ultrasound-guided ET have followed, which described the exact position of the catheter in the uterine cavity, emphasizing the need to avoid touching the fundus in order to enhance pregnancy rates after placing the embryos [21–24]. Franco *et al.* [8] later conducted a prospective study to determine the influence of the depth of embryo placement in the endometrial cavity on implantation and CPRs. Four hundred ETs guided by ultrasound were randomly assigned to two groups. Group 1 ( $n=200$ ) consisted of transfers corresponding to a distance of  $< 50\%$  of the ECL, which were transferred in upper half of the cavity and group 2 ( $n=200$ ) consisted of transfers corresponding to a distance of  $\geq 50\%$  of the ECL, in which the transfer was in the lower half of cavity. The authors concluded no significant difference in implantation or pregnancy rates between the two groups [8]. Franco *et al.* [8] have also recommended that further studies are needed to confirm whether there is an effect of site of ET on implantation rates [8]. Abou-Setta [25] performed a meta-analysis of randomized trials comparing different uterine deposition sites, ECL, and the distance from the fundus to the DTC. He performed meta-analysis on three studies and analyzed the live-birth rate (LBR), ongoing pregnancy rate (OPR), and CPR. When transfers were performed to the lower half of the uterine cavity, the LBR and OPR showed an increasing trend. For the DTC, all rates were significantly higher for the approximately 20 mm versus approximately 10 mm distance from the uterine fundus. He concluded that the results of the systematic review showed that there is limited evidence of the superiority of lower cavity transfers (e.g. approximately 20 mm) compared with the traditional high cavity (e.g. approximately 10 mm) transfers [25].

Another study that prospectively reviewed 104 embryo

transfers, matched the patients in two groups according to the distance between the tip of the catheter and the uterine fundus at transfer (group A  $> 10 < 15$  mm and group B  $\leq 10$  mm) and the same method of loading embryos into the ET catheter was used. Despite the similarity between the number and quality of embryos transferred, the CPRs varied significantly ( $p \leq 0.05$ ) between the two groups: 27.7% in group A and 14% in group B, there was no statistically significant difference in abortion rate and ectopic pregnancy rates between the two groups studied [26].

To further determine the best site for embryo placement in uterine cavities of varying shapes, a prospective study of 638 embryo transfers by Sun *et al.* [27] was conducted in two groups. Group 1 ( $n=558$ ) embryos were transferred into uterine cavities of normal shape and group 2 ( $n=80$ ) embryos were transferred into uterine cavities of abnormal shape. The uterine cavity was divided into upper, middle, and lower regions. There were no significant differences in rates of pregnancy or implantation among the three regions in group 1. However, the implantation rate in group 2 was highest when embryos were placed in the middle region of the uterine cavity: 28.8% compared with 6.8% and 8.3% for the upper and lower regions, respectively ( $p < 0.05$ ). They concluded that pregnancy outcomes do not depend on embryo placement in normal uterine cavities, but it improves when embryo placement is in the middle region of an abnormal uterine cavity [27].

Abdel Salam [28] conducted a prospective study on 90 patients to assess the depth of embryo transfer placement on implantation and CPRs in ICSI cycles. ET took place two to four days after oocyte retrieval under transabdominal ultrasound control. The inner ET catheter was advanced through the canal into the uterine cavity until it was approximately  $< 0.75$ ,  $0.75 \leq 1.5$  or  $1.5-2$  cm from the fundus. The studied groups were grouped based on the distance between the tip of the catheter and the uterine fundus at transfer; group 1  $< 0.75$  cm, group 2  $0.75 \leq 1.5$  cm, and group 3  $1.5-2$  cm. There was a significant difference between group 1 and other groups in terms of implantation and CPRs; 10.3% and 13.3%, respectively, in group 1; 26.7% and 53.3%, respectively, in group 2, 27.8% and 53.3%, respectively, in group 3 [28]. The author concluded that the depth of embryo placement inside the uterine cavity might influence implantation and pregnancy rates.

In 2012, another prospective study was performed in order to investigate the influence of the depth of embryo placement into the uterine cavity on the implantation rate after ET carried out under transabdominal ultrasound guidance [29]. One hundred and six patients were divided into two groups according to the distance between the tip of the catheter and the uterine fundus at the time of embryo deposition in the cavity. Group A:  $10 \pm 2.5$  mm; group B:  $15 \pm 2.5$  mm. The pregnancy rate was higher in group B, 46.2% in comparison to the 28.8% in group A ( $p < 0.05$ ). There was no significant difference in abortion rate between the

two groups. They concluded that pregnancy rate is significantly influenced by the depth of embryo placement inside the uterine cavity [29]. The authors suggested that depth of embryo placement inside the uterine cavity may influence the pregnancy rates in IVF cycles [29].

Due to the conflicting results on the optimal distance from the site of ET to the embryo-fundus distance and its relation to better pregnancy outcomes, Rovei *et al.* [30] further studied 1,184 patients undergoing a blind, clinical-touch ET of one to two fresh embryos. The embryos were loaded in a soft catheter and the embryo-fundus distance (EFD) was measured by transvaginal ultrasound. When the distance was between five and 15 mm, higher pregnancy and implantation rates were observed. The abortion rate was much higher when EFD was below five mm than when it was between five and 15 mm. The authors reported an overall higher ongoing pregnancy rate in the group of patients whose embryos were released between five and 15 mm from the fundal endometrial surface. They suggested that an optimal range of EFD seems to be between five and 15 mm, around the third fourth of the uterine cavity [30].

In 2013, analysis of 281 consecutive US-guided fresh ETs performed by a single physician was done prospectively, and the length of the uterine cavity (A), the distance between the fundal endometrial surface and the tip of inner catheter (B), the distance between the fundal endometrial surface and the air bubbles (C), and the PRs were recorded: 115 (40.9%) patients were pregnant. The clinical intrauterine pregnancy rates were 65.2%, 32.2%, and 2.6% in the < 10 mm, 10-20 mm, and 20 mm respectively, in the C distance group. The PR was considerably reduced in cases with >10 mm between the fundal endometrial surface and the air bubbles [31]. Therefore, PR can be determined by the position of the air bubble in relation to the position of the embryo at ET, where CPRs were higher in cases with air bubbles closer to the fundus and when the distance between the fundal endometrial surface and the tip of the inner catheter is 1.5-2cm [31].

Table 1 provides a summary of prospective studies that shows pregnancy and implantation rates in relation to the site of the embryo placement from the uterine fundus.

## Discussion

ET is a final stage in IVF/ICSI cycles and many variables have contributed to either its success or failure in terms of pregnancy rates [17]. Despite the fact that most patients will reach the ET stage and have the actual transfer, embryo implantation is another hurdle that defines success and thus pregnancy [32]. Therefore, embryos should be handled with caution and placed meticulously and accurately in the uterus for pregnancy to occur [33]. One of the crucial steps in IVF cycle remains to be the ET and great emphasis has been placed on the site of embryo placement within

the uterine cavity, which may influence both the embryo implantation rates and pregnancy rates. Initially, studies suggested that pregnancy rates are higher when embryos were positioned close to the fundal endometrial surface without touching the mucosa as to prevent any endometrial contraction [4].

This was followed by other studies that summoned the placement of embryos close to the uterine fundus around 10 mm below the fundal endometrial surface [16, 33] or close to the uterine fundus [34, 35]. Other authors have refuted those findings and suggested better pregnancy rates when embryos are placed at lower levels in the uterine cavity [16, 18, 19, 33, 36, 37]. The technical features of the oocyte recovery and ET were decisive to the accomplishment of a supported reproductive technologies program [38]. Subsequent studies concurred with these findings and reported higher PR when the catheter tip was positioned in the middle of the uterine cavity, approximately 15 mm from the fundal endometrium [10] or 15 to 20 mm from the fundal endometrium [10].

Cavagna *et al.* studied 63 pregnancies following ET to the middle point of the endometrial cavity. They reported 66.0% of the gestational sacs of singleton pregnancies were detected in the upper region, 29.8% in the middle region and 4.2% in the lower region. Similarly, pregnancy rates were 45.5, 51.5 and 3.0% respectively, for multiple pregnancies. Thus, higher pregnancy rates were reported when embryos were transferred to the central area of the uterine cavity [39, 40]. These findings were further accentuated with a meta-analysis that included three randomized prospective trials [8, 10, 16], which showed a higher pregnancy rate when embryos were placed in the middle of the uterine cavity (around 20 mm) in comparison to those placed close to the fundus (around 10 mm). To further elicit whether there is an optimal range of EFD within which embryos should be transferred and to optimize IVF outcome, Rovei *et al.* [30] conducted a large prospective study in which 1184 patients undergoing a blind, clinical-touch ET of one to two fresh embryos loaded in a soft catheter were recruited. The EFD was measured using transvaginal US performed immediately after ET. Higher pregnancy and implantation rates were detected when an EFD between five and 15 mm, which is approximately, third to fourth of the uterine cavity, was chosen in comparison to an EFD above 15 mm. The abortion rate was much higher when EFD was below five mm than when it was between five and 15 mm [30]. These reports were different than the results reported by other authors who suggested that the site of ET has no influence on implantation rates if placed in the upper half of the cavity [16, 41, 42].

Therefore, the IVF results can be affected by an important variable that is the site of the uterine cavity at which embryos are placed; however an exact and optimal site of where to release the embryos remains vague. This is mainly because even when the physicians intend to deposit the em-

Table 1. — Prospective studies that show pregnancy and implantation rates in relation to the site of the embryo placement from the uterine fundus.

Study	Type of the study	No. of patients	Depth in relation to the uterine cavity	Pregnancy rate	Implantation rate
[8] Franco (2004)	Prospective	400	Group 1 < 50% of the endometrial cavity length (ECL), i.e. transfer in upper half of the cavity; Group 2 (n = 200) consisted of transfers corresponding to a distance of > or = 50%, of the ECL, i.e. transfer in lower half of cavity.	No significant difference in pregnancy rates was observed between groups 1 and 2. Group 1: 35.0% (70/200) Group 2: 29.5% (59/200)	No significant difference in implantation rates was observed between groups 1 and 2. Group 1: 16.0% (89/555) and group 2: 16.4% (87/530)
[10] Frankfurter (2004)	Prospective	666	393 fundal and 273 lower to middle uterine segment ETs	Higher PR after middle to lower uterine segment ET compared with fundal ET (39.6% vs. 14%)	Higher implantation rates after middle to lower uterine segment ET compared with fundal ET (21% vs. 14%)
[25] Abou-Setta (2007)	Systematic review and meta-analysis	2,570	Assessments of the endometrial cavity length (ECL) and the distance from the fundus to the tip of the catheter (DTC) were utilized.	Pregnancy rates are similar when the upper and lower halves of the endometrial cavity are compared. Mid-cavity transfer (~20 mm) is superior to the traditional high transfer (~10 mm).	
[26] Pacchiarotti (2007)	Prospective	104	Two groups according to the distance between the tip of the catheter and the uterine fundus at transfer (group A > 10 < 15 mm and group B ≤ 10 mm).	Clinical pregnancy rates higher in group A (27.7%) vs. group B (14%).	
[27] Sun (2009)	Prospective	638	Group 1 (n=558) embryos were transferred into uterine cavities of normal shape; group 2 (n=80) embryos were transferred into uterine cavities of abnormal shape. For Group 1, the uterine cavity was divided into 3 equal regions: upper, middle, and lower.	No significant differences were found in rates of pregnancy among the 3 regions in group 1.	The implantation rate in group 2 was highest when embryos were placed in the middle region of the uterine cavity: 28.8% compared with 6.8% and 8.3% for the upper and lower regions, respectively ( $p < 0.05$ ).
[28] Mohamed (2010)	Prospective cohort	90	The patients were grouped according to the distance between the tip of the catheter and the uterine fundus at transfer (group 1 < 0.75 cm, group 2 0.75 ≤ 1.5 cm, group 3 1.5–2 cm)	PR higher in group II and III. Group 1: 13.3%, group 2: 53.3%, and group 3: 53.3%	Group 1: 10.3% Group 2: 26.7% Group 3: 27.8%
[29] Ivanovski (2013)	Prospective observational	106	The patients were divided into two groups according to the distance between the tip of the catheter and the uterine fundus at the time of embryo deposition in the cavity: group A: 10 ± 2.5 mm; group B: 15 ± 2.5 mm.	Pregnancy rate is significantly influenced by transfer distance from the fundus where the pregnancy rate decreases from Group A: 28.8% and group B: 46.2% ( $p < 0.05$ )	Ivanovski (2013)
[30] Rovei (2013)	Prospective	1,184	ET performed without any ultrasound guidance (clinical-touch ET, CTET). CTETs were classified into four subgroups according to the fundal endometrial surface (EFD): a) EFD < 5 mm (n=59); b) EFD between 5 and 9.9 mm (n=548); c) EFD between 10 and 15 mm (n=429); d) EFD > 15 mm (n=148).	Ongoing pregnancy rate was higher when the fundal endometrial surface (EFD) was between 5 and 15 mm. a) EFD < 5 mm (40.7 %%) b) EFD between 5 -9.9 mm (41.4%); c) EFD between 10–15 mm (43.4%); d) EFD > 15 mm (26.4%)	When EFD was between 5 and 15 mm, significantly higher implantation rates than an EFD above 15 mm. a) EFD < 5 mm (19.7%) b) EFD between 5 and 9.9 mm (20.9%); c) EFD between 10 and 15 mm (20.9%); d) EFD > 15 mm (12.9%)
[31] Cenksoy (2014)	Prospective	281	Position for embryo transfer divided in to 3 groups. A: from the uterine cavity B: the distance between the fundal endometrial surface and the tip of inner catheter C: the distance between the fundal endometrial surface and the air bubbles (C)	With regard to distance (C), the clinical intrauterine pregnancy rates were 65.2%, 32.2%, and 2.6% in the < 10-mm, 10-20-mm, and 20-mm distance groups, respectively. The PR was dramatically reduced in cases with >10mm between the fundal endometrial surface and the air bubbles. The optimal distance between the fundal endometrial surface and the tip of inner catheter is 1.5–2 cm.	



bryos at an exact distance from the uterine fundus or within an average distance of embryo deposition, endometrial wave contractions and hydraulic force may serve as unintended forces that may move the embryos closer or away from the projected site [25].

## Conclusions

In conclusion, the results of this review suggested that the site of the embryo deposition may affect the implantation and pregnancy rates. Most of the studies reviewed recommend positioning the tip of the catheter in the middle area of the endometrial cavity, around ten to 20 mm away from the fundus [25]. Implantation and pregnancy rates have been shown to be low when embryos are placed very close to the uterine fundus, less than five mm away from the fundus [2]. It has yet to be remembered that due to the heterogeneity of the reviewed studies and with the available conflicting evidence, it is possible that the site of ET affects IVF/ICSI outcome. It is also important to note that most studies have estimated the EFD according to the placement of the catheter tip during embryo injection and ignored the fact that the embryos may be placed a few mm closer to the uterine fundus than the catheter's tip while being injected [30]. Few studies have located the actual site of embryo release by ultrasound localization of the air bubble that is visible just after embryo release and not just the visualization of the catheter tip alone [30]. It is, therefore, recommended that physicians meticulously replace the embryos in the middle part of the uterine cavity; specifying the exact location where and how embryos are to be placed remains a challenging question that opts for a well-designed randomized controlled trial in order to define the optimum range of an EFD. Meticulous and precise replacement of the embryos within the endometrial cavity will remain the most crucial step in ET for better implantation and pregnancy rates.

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