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Best site for embryo transfer: the upper or lower half of endometrial cavity?

J.G.Franco Jr[1–3], A.M.V.C.Martins[2], R.L.R.Baruffi[1], A.L.Mauri[1], C.G.Petersen[1], V.Felipe[1], P.Contart[1], A.Pontes[2] and J.B.A.Oliveira[1]

[1]Center for Human Reproduction, Sinhá Junqueira Maternity Foundation, Ribeirão Preto, SP and [2]Department of Gynecology and Obstetrics, Faculty of Medicine of Botucatu, UNESP, Botucatu, SP, Brazil

[3]To whom correspondence should be addressed at: Center for Human Reproduction, Sinhá Junqueira Maternity Foundation, Rua D. Alberto Gonçalves, 1500 - CEP 14085-100, Ribeirão Preto, SP, Brazil. E-mail: crh@crh.com.br

BACKGROUND: The objective of the present study was to determine the importance of the site of embryo transfer (upper or lower half endometrial cavity) on implantation and clinical pregnancy rates. METHODS: A total of 400 transfers guided by ultrasound were randomly assigned to two groups according to the distance between the uterine fundus and the catheter tip at the time of embryo placement. Group I ($n = 200$) consisted of transfers corresponding to a distance of <50% of the endometrial cavity length (ECL), i.e. transfer in upper half of the cavity; and group II ($n = 200$) consisted of transfers corresponding to a distance of ≥50%, of the ECL, i.e. transfer in lower half of cavity. The Student's *t*-test, Mann–Whitney test and Fisher's exact test were used where appropriate. RESULTS: The general characteristics of the study population and the main transfer cycle characteristics had an equal distribution ($P > 0.05$) between groups I and II. No significant difference in implantation or pregnancy rates was observed between groups I and II. CONCLUSION: The implantation or pregnancy rates were similar whether the embryos were deposited in the upper or lower half of the endometrial cavity.

Key words: embryo transfer/endometrial cavity length/implantation rates/IVF/pregnancy rates

Introduction

The main variables that affect nidation are related to uterine receptivity, embryo quality and the efficiency of embryo transfer. Embryo transfer is the critical step in assisted reproductive technology, with rigid catheters, contamination with blood, mucus or bacteria, increased contraction waves of the myometrium, and the level of difficulty in introducing the catheter inside the uterine cavity tending to reduce embryo implantation rates (Goudas *et al.*, 1998; Lesny *et al.*, 1998; 1999; Schoolcraft *et al.*, 2001; Mansour and Aboulghar, 2002; Buckett, 2003; Levi Setti *et al.*, 2003; Mirkin *et al.*, 2003; Sallam and Sadek, 2003).

However, little attention has been paid to embryo transfer, a fact reflected in the scientific publications regarding this subject, which are rare compared with those evaluating other aspects of IVF. The probable reason is the apparent simplicity of this maneuver, since most clinicians do not consider inserting a catheter through the uterine cervix and ejecting embryos a difficult task. This facility, however, is relative.

Differences in individual transfer performances are reflected in the results reported in the literature. Meldrum *et al.* (1987) and Naaktgeboren *et al.* (1997) emphasized that meticulous embryo transfer is essential for the success of IVF. Assessing the question of the operator within the same program, Hearns-Stokes *et al.* (2000) found significant differences in pregnancy rates between 11 clinicians who performed 854 embryo transfers. In that study, all aspects of the IVF-embryo transfer cycle were standardized: the groups were homogenous in terms of all aspects including embryo quality, the number of embryos transferred and the transfer technique employed. Karande *et al.* (1999) reported significant differences in pregnancy rates between clinicians even when uniform protocols of ovarian stimulation and embryo culture were used. However, Visser *et al.* (1993) did not observe significant variations in pregnancy rates between three different clinicians.

Embryos are routinely transferred through the transcervical route, with the catheter being inserted in two ways: blindly by 'clinical touch' or guided by ultrasound. Many services use the 'sensitivity' of the clinician to place the embryos within the uterine cavity at a point close to the fundus (Salha *et al.*, 2001; Schoolcraft *et al.*, 2001), similar to the description published by Edwards more than 20 years ago. With respect to this type of embryo transfer, which is more traditional, no attempt has been made to document the variables that might have a negative impact and cause low pregnancy rates and failure of the whole process, such as inadvertent touch of the catheter tip on the fundal endometrial surface or inappropriate embryo placement in the uterine cavity (Woolcott and Stanger, 1997; Buckett, 2003; Levi Setti *et al.*, 2003; Sallam and Sadek, 2003).

Ultrasonographic observation has many potential advantages: it prevents touching the fundus of the uterus, it confirms that the catheter is beyond the internal orifice and it permits guidance of the catheter along the endometrial line, a fact that facilitates the use of more flexible catheters. In addition, the full bladder required for transabdominal ultrasound itself is useful for the correction of uterine access through the cervical route in cases of pronounced anteversion–anteflexion.

The use of ultrasound to assist embryo transfer was first described by Strickler *et al.* (1985), who reported that guided transfer is easier and less associated with catheter distortion. Later, several other studies showed that ultrasound-guided embryo transfer yields better implantation and pregnancy rates (Hurley *et al.*, 1991; Prapas *et al.*, 1995; Lindheim *et al.*, 1999; Coroleu *et al.*, 2000; 2002b; Wood *et al.*, 2000; Buckett, 2003; Levi Setti *et al.*, 2003; Mirkin *et al.*, 2003; Sallam and Sadek, 2003), in addition to facilitating the transfer procedure.

Furthermore, ultrasound provides new insights into the process of embryo transfer. One interesting aspect is the site in the endometrial cavity where the embryos are placed, with some reports correlating this variable with the site of implantation. Baba *et al.* (2000) analysed 60 embryo transfer that resulted in 22 pregnancies and 32 gestational sacs. Twenty-six of the 32 sacs were detected by three-dimensional ultrasound in the area where the air bubble had been observed immediately after transfer. Liedholm *et al.* (1980) placed small spheres in a column containing 50 μl of fluid and performed a simulated embryo transfer immediately before hysterectomy. The uterine cavity was then inspected and the microspheres were found within a distance of 1 cm from the presumed deposition site. These results emphasize the importance of the site where the embryos were transferred.

It has been traditionally accepted that embryos should be placed 5–10 mm below the surface of the uterine fundus. However, some investigators have suggested that placing embryos lower in the endometrial cavity may improve pregnancy rates. Waterstone *et al.* (1991) reported the results of embryo transfer performed by two clinicians who followed different techniques. The first introduced the catheter until he felt the fundus and then pulled it back 5 mm before injecting the embryos, and achieved a final pregnancy rate of 24%. The second clinician introduced the catheter until a depth of 5 cm from the external orifice of the cervix and deposited the embryos without touching the fundus, and obtained a pregnancy rate of 46%. When the first clinician modified his technique according to that of the second, improvement in pregnancy rates was observed.

Coroleu *et al.* (2002a) analysed 180 patients submitted to guided embryo transfer, with the transfers being divided into three groups according to the distance between the uterine fundus and the site of embryo placement: group 1, 10 ± 1.5 mm; group 2, 15 ± 1.5 mm; and group 3, 20 ± 1.5 mm. The best implantation and pregnancy rates were observed for groups 2 and 3, in which the distance from the uterine fundus was greater than in group 1.

Frankfurter *et al.* (2003) retrospectively analysed 23 patients who underwent two cycles of ultrasound-guided embryo transfer each, considering for each patient a transfer that resulted in pregnancy and one that did not. The results showed better pregnancy rates when the site of embryo placement relative to the length of the endometrial cavity was more distant from the uterine fundus. No significant difference was observed when comparing the absolute distance.

Based on the evidence discussed above, the objective of the present prospective study was to determine the influence of the depth of embryo placement in the endometrial cavity on implantation and clinical pregnancy rates after embryo transfer carried out under transabdominal ultrasound guidance.

Materials and methods

A total of 400 cycles of 360 patients enrolled in the IVF/ICSI program of the Center for Human Reproduction, Sinhá Junqueira Maternity Foundation, during the period from August 2001 to October 2003 were included in this study. Transfer cycles of frozen embryos were excluded. For the calculation of sample size, the current rate of pregnancy by transfer in our centre (~30%) was taken into consideration, so that to detect a difference of 15% on the pregnancy rate in each group (upper or lower cavity) with $\alpha = 0.05$ and β with power of 80%, we would need 200 cycles in each branch of randomization.

All patients were submitted to the same scheme of controlled ovarian stimulation (Franco *et al.*, 2001). First, pituitary blockade was established with nafarelin acetate at a dose of 400 μg/day (Synarel®; Searle Sao Paulo, Brazil.), started during the second phase of the previous cycle. After 14 days of treatment with the analogue and confirmation of blockade, administration of recombinant FSH (Gonal F®; Serono Barueri, SP, Brazil) was started at a dose of 150–300 IU depending on the age of the patient, for a period of 7 days. On the eighth day of stimulation, follicular development was monitored by 7 MHz transvaginal ultrasound only (Medison Digital Color MT; Medison Co. Ltd, Seoul, Korea) and the FSH doses were adapted according to ovarian response.

On the day of first ultrasound for the control of ovarian stimulation, the distance between the fundus of the uterine cavity (end of the endometrial image) and the internal ostium of the cervical canal was measured by transvaginal ultrasound. This parameter was called endometrial cavity length (ECL) (Figure 1).

When at least two follicles with a diameter ≥17 mm were observed, HCG was administered at a dose of 5000–10 000 IU. Oocytes were retrieved by transvaginal ultrasound-guided puncture 34–36 h after injection of HCG.

ICSI and IVF were performed as described previously (Franco *et al.*, 1995; Svalander *et al.*, 1995). Embryos were routinely transferred after 48 h in culture, and supranumerary embryos were cryopreserved at the end of the second day.

Embryos were then transferred with a Frydman catheter (Frydman® Classic Catheter 4.5 CCD Laboratoire C.C.D; Paris, France) guided by abdominal ultrasound using a 3.5 MHz convex transducer (Aloka SSD-1100; Aloka Co. Ltd, Tokyo, Japan). On the day of embryo transfer, the patients were randomized by drawing lots before the procedure using a table previously designed for the study. The patients were allocated to two groups according to

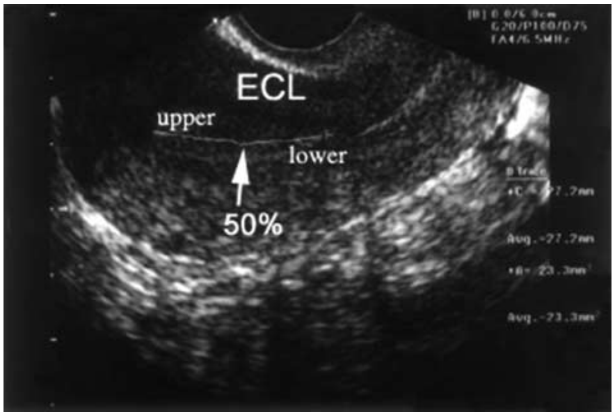

Figure 1. Measurement of the uterine cavity by vaginal ultrasound.

the distance between the catheter tip and the uterine fundus at the time of embryo transfer.

Group I: image corresponding to the catheter tip at upper half of endometrial cavity, i.e. at any point <50% of the ECL measurement (Figure 2). This group consisted of 200 embryo transfer from 192 patients.

Group II: image corresponding to the catheter tip at the lower half of endometrial cavity, i.e. at any point ≥50% of the ECL measurement (Figure 3). Included in this group were 200 embryo transfer from 191 patients. It should be noted that the same patient in different cycles might have been randomized to either group I or group II.

All transfers were performed by a single physician, and only easy transfers (i.e. the catheter passed smoothly through the cervix without the need for uterine fixation clamps) with clear visualization of the catheter tip upon ultrasound were considered for analysis. The preparation for embryo transfer was the same for the two groups. Patients with a full bladder were placed in the lithotomy position and the cervix was exposed using a bivalve speculum. The exocervix was cleaned and endocervical mucus was removed with a sterile catheter connected to a syringe containing culture medium.

The same transfer technique was maintained for all patients. The catheter was first filled with Irvine P1 transfer medium (Irvine Scientific Santa Ana, CA, USA) supplemented with 10% human serum albumin. Next, the transfer medium containing the embryos was loaded into the catheter between air bubbles and, finally, more transfer medium was added (maximum total volume 30 μl). The catheter was introduced into the endometrial cavity through the cervix under ultrasound guidance up to the point estimated for transfer. The distance between the end of the fundal endometrial surface and the catheter tip was then again measured by ultrasound and considered for analysis of the results.

Figure 2. Higher transfer: ultrasound-guided embryo transfer showing the tip of the catheter (arrowhead) inserted into the uterine cavity at a distance of 13 mm from the fundal endometrial surface.

Figure 3. Lower transfer: ultrasound-guided embryo transfer showing the tip of the catheter (arrowhead) inserted into the uterine cavity at a distance of 17 mm from the fundal endometrial surface.

In all transfers, the medium containing the embryos was gently expelled into the uterine cavity under ultrasound monitoring, with the volume being sufficient to permit the ultrasonographic visualization of the transfer inside the uterine cavity, which was also facilitated by the presence of air bubbles between the embryos ('transfer bubbles'). The catheter was immediately and carefully removed after transfer, and analysed under a stereomicroscope to ensure that all embryos had been transferred. After the procedure, the patient was allowed to rest in bed for 60 min.

All patients received luteal phase supplementation with vaginal natural progesterone or additional doses of HCG according to ovarian response.

Pregnancy was diagnosed based on an increase in serum β-HCG concentration 15 days after embryo transfer. Implantation and clinical pregnancy rates were determined based on the presence of a gestational sac accompanied by an image of the embryo/fetal cardiac activity on transvaginal ultrasounds 4 weeks after transfer. The frequency of miscarriage and ectopic pregnancy was calculated based on the number of clinical pregnancies found.

The following parameters were evaluated in each group: patient age, aetiology of infertility, ECL (mm), number of oocytes retrieved by puncture, number of oocytes in metaphase II retrieved by puncture, fertilization rate, number of embryos transferred, distance in mm between the uterine fundus and the catheter tip at the time of transfer, embryo implantation rate, pregnancy rate per transfer, miscarriage rate, rate of ectopic pregnancies, and ongoing pregnancy rate.

Data are reported as means ± SD and were analysed using the InStat 3.0 program for MacIntosh (GraphPad Software, San Diego, CA, USA). The Student's *t*-test, Mann–Whitney test and Fisher's exact test were used where appropriate. The level of significance was set at $P < 0.05$.

Table I. General characteristics of the study population

Characteristic	
Patients (n)	360
Cycles (n)	400
Age (years) (± SD) (range)	34.1 ± 4.9 (19–44)
Aetiology	
Male	37.8% (136/360)
Idiopathic	25.8% (93/360)
Endometriosis	13.6% (49/360)
Tuboperitoneal	11.7% (42/360)
Tuboperitoneal + male	5.3% (19/360)
Tuboperitoneal + endometriosis	4.4% (16/360)
Endometriosis + male	1.1% (4/360)
Endometriosis + male + tuboperitoneal	0.3% (1/360)
ECL (mm) (± SD) (range)	30.7 ± 4.0 (22.3–44.6)
Retrieved oocytes (± SD) (range)	9.7 ± 5.6 (1–36)
Oocytes in metaphase II (± SD) (range)	7.4 ± 4.4 (0–29)
Fertilization (%) (± SD) (range)	73.5 ± 19.6 (16.6–100)
Embryo transfer (n) (± SD) (range)	2.7 ± 1 (1–7)
Distance (mm) where catheter tip stopped (± SD) (range)	15.8 ± 3.5 (10–34)
Distance (%) where catheter tip stopped (± SD) (range)	52.7 ± 9.7 (29.4–90.6)
Implantation rate (%)	16.2 (176/1085)
Pregnancy rate/transfer (%)	32.2 (129/400)
Miscarriage rate (%)	15.5 (20/129)
Ectopic pregnancy rate (%)	0.8 (1/129)
Ongoing pregnancy rate (%)	27% (108/400)

ECL = endometrial cavity length.

Results

The general characteristics of the study population are summarized in Table I.

An equal distribution ($P > 0.05$) of the main transfer cycle characteristics was observed for groups I and II (Table II). The transfer embryo mean in each group was: 2.7 ± 0.9 for group I and 2.6 ± 0.9 for group II. The difference was not significant between the two groups; however, 20% of the studied population was aged ≥40 years. There were two cases, one aged 44 and another aged 43, where a high number of embryos was transferred (patient aged 44 years, six embryos; patient aged 43 years, seven embryos). This fact defined the superior limit of embryos transfer in both groups (group I, one to six transfer embryos; group II, one to seven transfer embryos). On the other hand, in group I a total of 39.8% of transfers were two embryos, 37.8% were three embryos and 18.4% were four or more embryos (mainly in the population aged ≥40 years); in group II 44.3% of transfers were of two embryos, 34.0% were three embryos and 15.3% were four or more embryos (mainly in the population aged ≥40 years).

As expected, the position of the catheter tip in relation to the fundal endometrial surface differed significantly between groups I and II ($P < 0.001$), supporting the validity of the investigation.

No significant differences were observed between groups I and II regarding the rates of implantation, pregnancy, spontaneous miscarriage, ectopic pregnancy or ongoing pregnancy ($P > 0.05$) (Table III).

Discussion

Among the various aspects of embryo transfer, the site of embryo placement in the uterine cavity has been postulated to influence embryo implantation rates. Whereas some investigators believe that higher levels in the endometrial cavity closer to the uterine fundus lead to higher rates (Meldrum *et al.*, 1987; Krampl *et al.*, 1995), others have suggested that improved embryo transfer results are obtained when the embryos are placed at lower levels in the uterine cavity (Waterstone *et al.*, 1991; Naaktgeboren *et al.*, 1997; Woolcott and Stanger, 1997; Lesny *et al.*, 1998; Naaktgeboren *et al.*, 1998; Coroleu *et al.*, 2002a; Frankfurter *et al.*, 2003; van de Pas *et al.*, 2003). Finally, some authors postulate that the question regarding the site of embryo transfer does is of no importance since it does not influence implantation as long as embryos are placed in the upper half of the cavity (Nazari *et al.*, 1993; Roselund *et al.*, 1996). However, many of these studies were based on retrospective observations and/or were not supported by ultrasound at the time of transfer.

Since the beginning of the therapeutical application of IVF, many programs have followed in an empirical, but traditional, manner the method of ‘clinical touch’. This technique consists of the insertion of a catheter into the cavity until touching the fundal endometrium, followed by a 5/10 mm retreat and subsequent deposition of the embryos. This method was first described by Steptoe and Edwards but, despite being the best known technique for embryo transfer, its difficulties and uncertainties have been widely questioned. One of these uncertainties is related to the fact that transfers based only on the sensitivity of the operator are associated

Table II. Upper half × lower half: general characteristics of the two groups studied

	Group I: upper half	Group II: lower half	P
Patients (n)	192	191	
Cycles (n)	200	200	
Age (years) (± SD) (range)	34.0 ± 5.0 (19–44)	34.2 ± 4.8 (22–43)	0.77
ECL (mm) (± SD) (range)	29.7 ± 3.3 (22.3–40.0)	30.3 ± 3.6 (22.7–44.6)	0.06
Distance (mm) TC stopped (± SD) (range)	13.3 ± 1.6 (10–19)	18.3 ± 3.2 (13–34)	<0.0001
Distance (%) TC stopped (± SD) (range)	45.0 ± 3.8 (29.4–50)	60.3 ± 7.6 (50.1–90.6)	<0.0001
Retrieved oocytes (± SD) (range)	9.4 ± 5.5 (1–36)	9.9 ± 5.7(1–27)	0.37
Oocytes in metaphase II (± SD) (range)	7.3 ± 4.2 (1–29)	7.5 ± 4.6 (0–25)	0.62
Fertilization (%) (± SD) (range)	74.6 ± 20.3 (16.6–100)	72.3 ± 18.9 (16.6–100)	0.23
Embryo transfer (n) (± SD) (range)	2.8 ± 0.9 (1–6)	2.6 ± 1 (1–7)	0.19

ECL = endometrial cavity length; TC = tip of catheter.

Table III. Upper half × lower half: rates of implantation, clinical pregnancy, spontaneous abortion (≤12 weeks), ectopic pregnancy and ongoing pregnancy in the two groups studied

	Group I: upper half	Group II: lower half	*P*
Implantation rate	16.0% (89/555)	16.4% (87/530)	0.86
Pregnancy rate/transfer	35.0% (70/200)	29.5% (59/200)	0.28
Miscarriage rate	15.7% (11/70)	15.2% (9/59)	1.00
Ectopic pregnancy rate	1.4% (1/70)	− (0/59)	1.00
Ongoing pregnancy rate	29% (58/200)	25% (50/200)	0.43

with discrepancies between the presumed and true position of the catheter, especially considering the different levels of clinical experience (Hurley *et al.*, 1991; Woolcott and Stanger, 1997; Buckett, 2003; Levi Setti *et al.*, 2003; Sallam and Sadek, 2003).

On the other hand, ultrasound-guided embryo transfer ensures the exact position of the catheter in the uterine cavity (and, consequently, the site where the embryos will be transferred and probably implant), in addition to preventing touching the fundal area and thus the occurrence of bleeding and uterine contractions (Baba *et al.*, 2000; Coroleu *et al.*, 2000; 2002b; Wood *et al.*, 2000; Buckett, 2003; Mirkin *et al.*, 2003; Levi Setti *et al.*, 2003; Sallam and Sadek, 2003). In the present study, the embryos were accurately placed in the uterine cavity at the desired levels as determined by ultrasound, a fundamental point of this investigation. In addition, patients were randomized, thus balancing IVF variables. Furthermore, all transfers were performed by the same clinician, thus preventing the impact of the 'physician factor' on implantation rates (Karande *et al.*, 1999; Hearns-Stokes *et al.*, 2000). Likewise, to avoid interferences with the results, only one type of catheter was used, only embryo transfers considered to be easy were included and a strict transfer protocol was followed. On this basis, the two groups studied were also homogenous in terms of the embryo transfer variables themselves.

In the present study, no significant differences were observed between groups I and II, as expected when analysing variables such as patient age, classification and aetiology of infertility, number of retrieved oocytes, number of retrieved oocytes in metaphase II, fertilization rate or number of embryos transferred. Similarly, no difference in implantation, pregnancy or ongoing pregnancy rates was observed between the two groups when embryos were transferred to the upper or lower half of the endometrial cavity.

Thus, we conclude that considering transfers to upper or lower half of the endometrial cavity is not an important factor for implantation and pregnancy outcome. This conclusion is further supported by the large number of samples studied (400 cycles), a value higher than those reported in similar studies (Coroleu *et al.*, 2002a; Frankfurter *et al.*, 2003). However, it should be noted that to detect a difference between the two study groups avoiding a β-type error (maintaining the same pregnancy rates/transfer in the two groups), a great number of cycles would be necessary. The final result, although it is not definitive from a statistical point of view (total acceptation of the null hypothesis), evidences that such an end point (difference of 5% in the clinical pregnancy between upper and lower transfer) may not have practicable, because we would need 1371 cases in each branch for total statistical satisfaction.

Finally, the spontaneous abortion rate observed in the present study was similar to those reported in statistical investigations on assisted reproduction (Nygren and Andersen, 2001; Red Latinoamericana de Reproducción Asistida, 2001; ASRM/SART Registry, 2002), with no difference being observed between group I and group II. Since low implantation is a common finding in pregnancies that are eventually aborted, it has been suggested that the placement of embryos at lower points may be responsible in part for the high rate of spontaneous abortion. Since, in clinical practice, transfers were performed close to the central region of the endometrial cavity in most cycles, the abortion rate might have been influenced. On the other hand, it has been speculated that careful expulsion of the transfer medium to the potential implantation site under ultrasonographic vision prevents reflux of the medium containing the embryos, a fact leading to low implantation and abortion.

Previous studies have reported an increased risk of ectopic pregnancies in cases of transfers close to the uterine fundus (Yovich *et al.*, 1985; Nazari *et al.*, 1993; Lesny *et al.*, 1998; 1999; Egbase, 2000). In the present study, only one ectopic pregnancy was observed in the group in which the transfer occurred in the upper half (group I).

In conclusion, the present results demonstrate that implantation and pregnancy rates are not influenced by whether the embryos were deposited in the upper or lower half of endometrial cavity. However, further studies are needed to confirm whether or not there is an effect of site of embryo transfer on implantation rates, in order to provide data that lead to qualitative improvement in clinical strategies.

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