Transvaginal versus transabdominal ultrasound guidance for embryo transfer in donor oocyte recipients: a randomized clinical trial

Daniel Bodri, M.D., M.Sc., Ph.D.,[a] *Marta Colodrón, M.D.,*[a] *Désirée García, Pharm.D.,*[b] *Albert Obradors, M.Sc., Ph.D.,*[a] *Valérie Vernaeve, M.D., Ph.D.,*[a] *and Oriol Coll, M.D., Ph.D.*[a]

[a] Clínica EUGIN; and [b] Fundació privada Eugin, Barcelona, Spain

Objective: To compare pregnancy and implantation rates with transvaginal (TV) versus transabdominal (TA) ultrasound-guided embryo transfer (ET).
Design: Randomized, clinical trial registered at clinicaltrials.gov (NCT 01137461).
Setting: Private, infertility clinic.
Patient(s): Three-hundred thirty randomized recipients of donor oocytes.
Intervention(s): Embryo transfer using TV (with empty bladder, using the Kitazato ET Long catheter) versus TA ultrasound guidance (with full bladder, using the echogenic Sure View Wallace catheter).
Main Outcome Measure(s): Overall pregnancy, clinical pregnancy, implantation, and ongoing pregnancy rates. Duration and difficulty of ET. Patient-reported uterine cramping and discomfort, as evaluated by questionnaire.
Result(s): No statistically significant differences were observed in clinical pregnancy 50.9% versus 49.4% (95% confidence interval of the difference: −9.2 to +12.2%), implantation 34.5% versus 31.4% (95% CI of the difference: −4 to +10.3%) between the TV and TA ultrasound-guided groups. Transfer difficulty (6% versus 4.2%) and uterine cramping (27.2% versus 18.3%) were not statistically significantly different between treatment groups. Total duration (154 ± 119 versus 85 ± 76 seconds) was statistically significantly higher in the TV ultrasound group. Light to moderate-severe discomfort related to bladder distension was reported by 63% of the patients in the TA ultrasound group.
Conclusion(s): Transvaginal ultrasound-guided ET yielded similar success rates compared with the TA ultrasound-guided procedure without requiring the assistance of a sonographer. It was associated with increased patient comfort due to the absence of bladder distension. (Fertil Steril® 2011;95:2263–8. ©2011 by American Society for Reproductive Medicine.)

Key Words: Embryo transfer, in vitro fertilization, oocyte donation, transabdominal ultrasound, transvaginal ultrasound

In recent years, the importance of embryo transfer (ET) has been increasingly recognized, and its numerous technical aspects have therefore been scrutinized. One of the factors that may improve the outcome of the procedure is the use of ultrasound guidance (1). Evidence emerging from 17 to 20 randomized controlled trials comparing ultrasound guidance versus the "clinical touch" method for ET was evaluated in three meta-analyses (2–4). In all three of them, clinical pregnancy rates were found to be statistically significantly higher (odds ratio 1.31–1.50) with transabdominal (TA) ultrasound guidance.

Transvaginal (TV) ultrasound guidance was first described in the 1990s (5, 6). A large retrospective Japanese study involving 846 cycles showed higher pregnancy and implantation rates with the use of TV ultrasound guidance (7). Another retrospective study performed in 129 in vitro fertilization (IVF) patients suggested that TV ultrasound-guided transfer might be beneficial in patients with previous failed cycles (8). Recently, TV was compared with TA ultrasound guidance in the first published randomized clinical trial yielding comparable pregnancy rates (9). Whereas all the previous studies evaluated nondonor IVF patients, we have used the oocyte donation recipient population to evaluate the two different ET techniques. In fact, oocyte donation provides a unique model to eliminate confounding variables that typically occur when comparing nondonor IVF patients (10). The present randomized clinical trial was based on a hypothesis of equivalence between the two ultrasound guidance techniques with the additional aim of confirming potential benefits of the TV approach (more patient comfort, no need for sonographer).

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Reprint requests: Daniel Bodri, M.D., M.Sc., Ph.D., Clínica EUGIN, calle Entença 293-295, 08029 Barcelona, Spain (E-mail: bodridaniel@gmail.com).

MATERIALS AND METHODS

Study Characteristics, Patient Inclusion and Exclusion Criteria

Patients undergoing oocyte donation treatment at a single infertility centre between July and October 2010 were prospectively recruited in the present randomized clinical trial. Recipients undergoing fresh ET with two cleavage-stage (days 2 to 3) embryos were eligible. Black recipients, Turner

syndrome patients, or those with uterine malformations/fibroids were not eligible due to lower expected pregnancy rates (11–13). These specific recipient groups represent a minority in our general recipient population. The trial was approved by an external ethics committee (CEIC IDIAP Jordi Gol i Gurina, Barcelona, Spain) and was registered at clinicaltrials.gov (NCT 01137461).

Oocyte Donation Treatment

The donors' ovarian stimulation was conducted with a gonadotropin-releasing hormone (GnRH) antagonist protocol coupled with GnRH agonist triggering (14). Before treatment, careful clinical assessment was carried out in oocyte recipient candidates. The uterine cavity was assessed in 79% of the patients by a hysterosalpingography or hysteroscopy. Patients did not undergo mock transfer before their ET procedure; nonetheless, 61% had already undergone one or more ET cycles during previous infertility treatment attempts. Oral estradiol valerate or transdermal estradiol patches were used in a constant dose (6 mg/day or 150 μg/every 3 days) regimen for endometrial preparation, and the duration of the treatment varied in accordance with the availability of the oocytes. From the day of the oocyte retrieval from the donor, 800 mg/day of micronized vaginal progesterone was added. In case of pregnancy, hormone replacement therapy was continued for 70 days after embryo replacement. The laboratory procedures and combined embryo score used have been described previously elsewhere (15).

Informed Consent and Randomization

Eligible patients were informed of the possibility of participating in the clinical trial 2 to 3 days before the scheduled ET. On the day of the ET, a signed consent form was collected from those recipients who confirmed their participation. These patients were randomized immediately before the ET procedure by a dedicated study monitor (D.G.). The computer-generated randomization list was password protected and accessible only to the study monitor. All ET procedures were performed by two experienced operators (D.B. and M.C.) in a 60% to 40% proportion: 102 versus 96 and 63 versus 69 ETs with the TV and TA approaches by operator 1 and 2, respectively. The acquisition of study data was uniquely performed by the study monitor. The operators were blinded for outcome data until the completion of the procedural part of the trial.

Embryo Transfer Technique

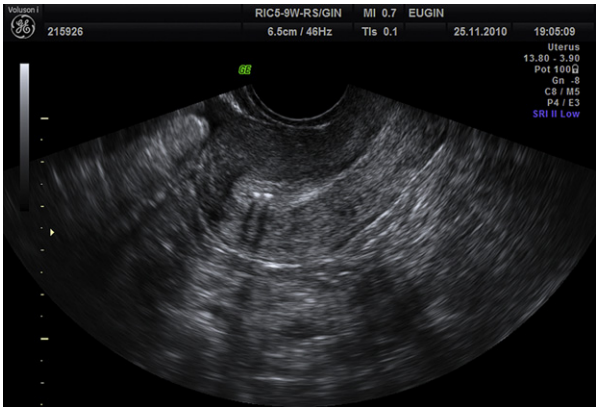
Ultrasound equipment, and the pretransfer and posttransfer events are described in the supplementary materials and methods section (available online). The TV ultrasound-guided ET was performed with a slight modification (removal of the speculum) to the protocol used routinely at the Kato Ladies Clinic (Tokyo, Japan). The position of the uterus (anteverted, intermediate, or retroverted), configuration of the cervical canal (length, curve), and endometrial thickness were evaluated with an initial, short TV ultrasound scan. The physician inserted a sterile Collin vaginal speculum; the cervix was exposed and gently cleansed with sterile gauze pads. The transfer procedure was performed using a two-stage technique ("afterloading") in close collaboration with the embryologist. The Kitazato ET Long catheter (no. 233340; Kitazato Medical Co., Ltd., Tokyo, Japan) is composed of a semirigid, 20 cm-long, 3F, precurved (30°) outer sheath with a soft obturator and very thin, hyperflexible, 40-cm-long, soft silicone inner catheter. The outer sheath with a small ball-shaped tip was inserted into the cervix until it reached the internal os. Subsequently, the speculum was gently removed, and a covered vaginal ultrasound probe was inserted in the vagina by concomitantly maintaining the already inserted ET catheter in its cervical position. The correct position of the catheter in relation to the internal os was verified on the scan, and a sagittal plane of the uterine body showing the whole endometrial lining was obtained. The soft obturator was removed from the inserted outer sheath.

At the physician's signal, the embryologist started to load the embryos into the soft inner catheter. When finished, the embryologist brought the loaded inner catheter and inserted it into the outer sheath, which was maintained in its position by the physician. Afterward, while holding with one hand the probe and the end of the outer sheath, under continuous TV ultrasound control, the readily visible inner catheter was advanced to within a 10 to 20 mm distance of the uterine fundus by the physician. Finally, at the physician's signal, an approximately 0.1-μL media volume was injected by the embryologist.

The appearance of two echogenic spots generated by the two loaded air bubbles was observed on the scan, which marked exactly (between the two spots) the site of embryo deposition (Fig. 1). The inner catheter was immediately removed. Any retained embryos were immediately retransferred using the same technique. The TA ultrasound-guided ET is the center's standard approach and was performed with the Sure View Wallace Embryo Replacement Catheter and full bladder (described in detail in the supplementary materials and methods section).

FIGURE 1

Transvaginal ultrasound image of the uterus after injecting the embryos with the Kitazato ET Long catheter.



Bodri. Transvaginal ultrasound-guided ET. Fertil Steril 2011.

Sample Size Calculation and Outcome Measures

Power analysis showed that (based on the center's clinical pregnancy rate of 49% during 2009) with an estimated 165 patients in each treatment arm the study would have 80% power to show equivalence between the two ultrasound groups with a margin of ±15%, at a two-sided statistical significance level of 5%. This fairly large equivalence margin was chosen based on data of a previous small nonrandomized pilot study performed in our center (16) where clinical pregnancy rates were found to be in favor (14.5% higher) of the TV group. In contrast, by choosing a smaller ±5% equivalence margin, a prohibitively large sample of more than 3,120 patients would have been required, which was not feasible in the setting of a single center study. Primary outcome measures were overall pregnancy, clinical pregnancy, implantation rates, and ongoing pregnancy rates. Secondary measures were the duration and difficulty of ET. Their definitions and the patient questionnaire used are described in the supplementary materials and methods section.

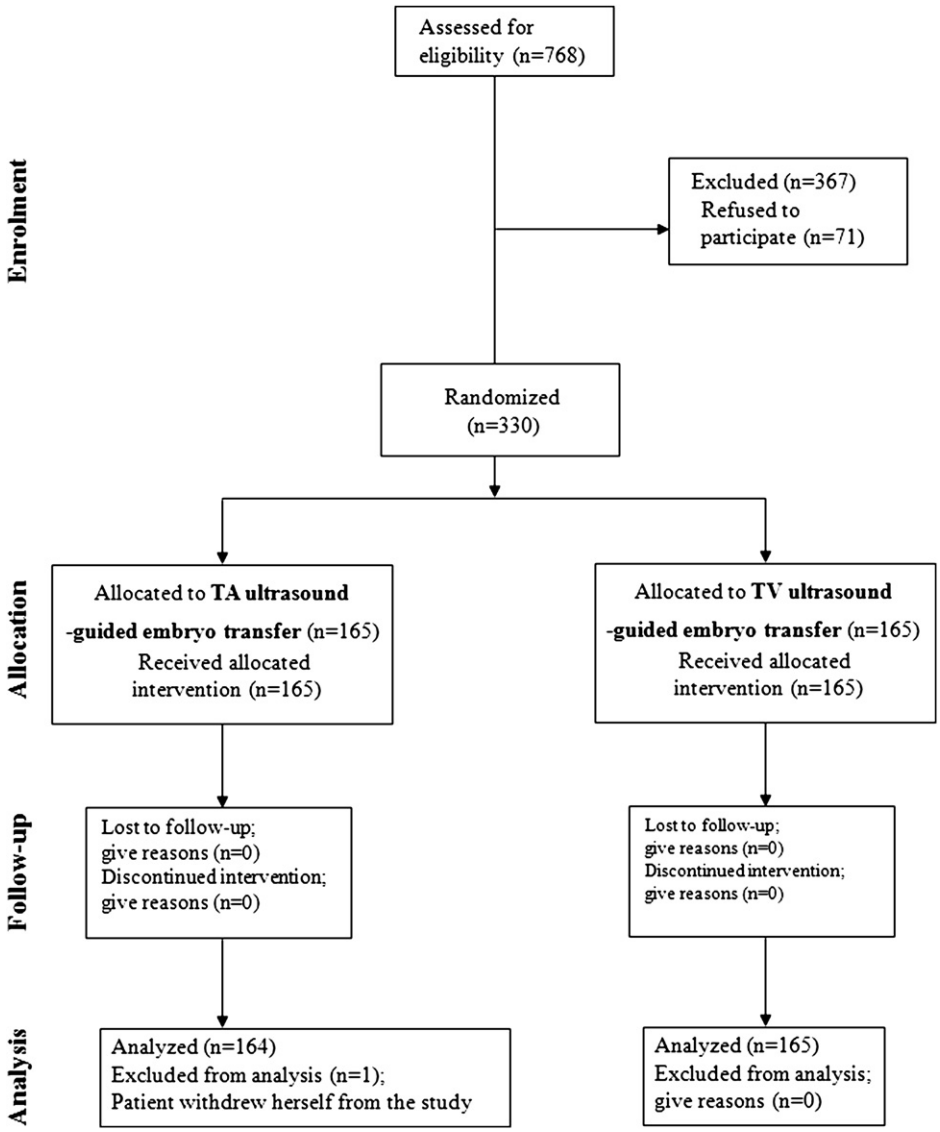
RESULTS

A total of 768 recipients were assessed for eligibility, and 401 were approached to participate in the trial. Seventy-one of these women (17.7%) refused to participate. Consequently, 330 were randomized to receive ET guided by TV (n = 165) or TA ultrasound (n = 165). One (0.6%) patient in each treatment group received the opposite technique, as intended. Outcomes from these two patients were analyzed in their original group according to the intention-to-treat principle (Fig. 2).

No differences were observed in recipients or their male partners' characteristics or cycle-related variables between treatment groups (Tables 1 and 2). The difference in endometrial thickness reached limited statistical significance. No statistically significant differences were observed in overall pregnancy (61.8%, 102 of

FIGURE 2

Patient flow according to the CONSORT statement flow diagram.



Bodri. Transvaginal ultrasound-guided ET. Fertil Steril 2011.

165 vs. 58.5%, 96 of 164) (95% confidence interval [CI] of the difference: −7.2 to +13.7%), clinical pregnancy (50.9%, 84 of 165 vs. 49.4%, 81 of 164) (95% CI of the difference: −9.2 to +12.2%), implantation (34.5%, 114 of 330 vs. 31.4%, 103 of 328) (95% CI of the difference: −4 to +10.3%), or ongoing pregnancy rates (43%, 71 of 165 vs. 42.7%, 70 of 164) (95% CI of the difference: −10.2 to +10.9%) between the TV and TA ultrasound-guided groups. One (0.6%) extrauterine pregnancy occurred in the TA ultrasound group. The twinning, biochemical pregnancy, and miscarriage rates were comparable (see Table 2).

The total duration of ET (154 ± 119 vs. 85 ± 76 seconds, $P<.0001$) was statistically significantly higher in the TV ultrasound group. Both catheterization (76 ± 116 vs. 33 ± 65 seconds, $P<.0001$), embryo loading (49 ± 20 vs. 33 ± 13 seconds, $P<.0001$), and injection times (28 ± 14 vs. 20 ± 25 seconds, $P<0.0001$) were higher in the TV ultrasound group.

No differences were observed in the rate of difficult transfer procedures (6% vs. 4.2%, $P=.47$) or embryo retention (1.8% vs. 3.6%, $P=.32$). Patient-reported uterine cramping (27.2% vs. 18.3%, $P=.11$) was comparable between the treatment groups. As expected, in the TA ultrasound group 41%, 16%, and 6% (a total 63%) of the patients reported light, moderate, and severe discomfort related to bladder distension, respectively.

DISCUSSION

This randomized clinical trial found no statistically significant difference in pregnancy or embryo implantation rates in donor oocyte recipients undergoing ET with TV versus TA ultrasound guidance. We found that TA ultrasound guidance was associated with increased patient discomfort related to bladder distension, which was avoided by the TV approach.

TABLE 1

Transvaginal versus transabdominal ultrasound-guided transfer: recipients' and their partners' characteristics.

	Transvaginal ultrasound	Transabdominal ultrasound	*P* value
No. of recipients	165	165	—
Age (y)	40.3 ± 4.9	40.4 ± 4.7	.88[a]
BMI (kg/m^2)	23 ± 3.7	23.7 ± 4.4	.15[a]
Cycle rank			.17[b]
First	128 (78)	123 (75)	—
Second	28 (17)	38 (23)	—
Third or fourth	9 (5)	4 (2)	—
Indication for oocyte donation			.47[b]
Reduced ovarian reserve, n (%)	132 (80)	128 (78)	—
Early/natural menopause, n (%)	21 (13)	17 (10)	—
Previous IVF failures, n (%)	11 (6)	18 (11)	—
Other, n (%)	1 (1)	2 (1)	—
No. of recipients' partners	148	151	—
Partner age (y)	40.5 ± 6.5	40.5 ± 6.1	.93[a]
Patients with normozoospermia, n (%)	39 (23)	31 (19)	.42[b]
Patients with abnormal sperm parameters, n (%)[c]	109 (66)	120 (73)	—
Donor sperm, n (%)	17 (11)	14 (8)	—

Note: Values are mean ± standard deviation. BMI = body mass index.

[a] Independent *t*-test.

[b] Chi-square test.

[c] Oligo-, astheno-, teratospermia or combination of these anomalies, according to WHO 1999 Guidelines.

Bodri. Transvaginal ultrasound-guided ET. Fertil Steril 2011.

The TV approach might have a number of potential benefits that were partially demonstrated in the present clinical trial. Discomfort of varying degrees related to bladder distension was frequently reported by patients in the TA arm, which was evidently avoided using the TV approach requiring a fully emptied urinary bladder. A previous study already demonstrated that the degree of bladder distension correlates with pain or discomfort reported by patients during ET (17). Furthermore, the issue of obtaining optimal bladder distension (including the need for patient instructions and possible extra waiting time if bladder distension is insufficient) could also have a major impact on the everyday management of a busy clinic. Application of TA ultrasound requires the presence and adequate training of an additional person (e.g., a nurse or sonographer). This contrasts with the TV approach where the scanning is easily performed by the operator. In our study, a lower incidence (although not statistically significant) of embryo retention and extrauterine pregnancy rate was observed in the TV arm, which might be related to a more precise positioning of the catheter tip. Also, TV ultrasound, due to its higher resolution, frequently permits a "high-definition" view of the ET procedure (see Fig. 1), which is highly reassuring both for the patient and the operator. Although it was not evaluated in our study, TV ultrasound-guided ET might be particularly advantageous in cases when ultrasound visualization with the TA approach is suboptimal (e.g., in obesity or uterine retroversion). Hence, the TV ultrasound-guided ET technique might change clinical practice patterns by offering an efficient alternative to TA ultrasound-guided ET and potentially contributing to ET optimization and increased patient comfort.

The total duration of ET was statistically significantly higher in the TV arm of the study. This is easily explained if one takes into account that both at the initial catheterization and the final injection stages some extra time is needed to insert the vaginal probe and to obtain the correct sagittal plane of the uterus by slightly adjusting the position of the probe. Nonetheless, this additional time did not influence outcome because the average time interval between embryo loading and discharging in both treatment arms remained below the 2-minute time limit that has been previously shown to be a requisite to obtaining optimal pregnancy rates (18). In both treatment arms, a two-stage "afterloading" technique was used, which is the standard approach in our center. In relation to the TV approach, this two-stage technique is essential because it allows the operator to perform the first, slightly more complicated part of technique (catheter insertion and correct positioning of the ultrasound probe) without the presence of loaded embryos. Independent of the type of ultrasound guidance used, the afterloading technique also has advantages such as reducing the exposure of embryos to the external environment and aiding the training of less experienced operators (19).

Consistent with our findings, the first randomized clinical trial that directly compared the TV versus the TA approach for ultrasound guidance—involving a total of 186 randomized IVF patients—found equally high pregnancy rates in each treatment arm. The investigators concluded that neither of the two techniques provided better pregnancy rates and that uterine position, parity, and physician's preference should dictate the choice between the two approaches (9). In contrast to our trial, they did not find any difference in pain reported by their patients, but they did not try to differentiate between uterine cramping and discomfort related to bladder distension. The duration for ET was no longer for the TV approach in their trial. It was however comparable with the transfer duration of our TV arm (130 ± 176 vs. 154 ± 119 seconds). Another major difference in their trial was that all patients underwent a double mock transfer (with full and then empty bladder); also, two different catheters (Wallace and Cook Echotip) were used within the same group, and three operators performed the procedures. Moreover, as a further difference with the study of Porat et al. (9), in

TABLE 2

Transvaginal versus transabdominal ultrasound-guided transfer: cycle-related and outcome data.

	Transvaginal ultrasound	Transabdominal ultrasound	*P* value
No. of recipients	165	165	—
Endometrial preparation			.36[a]
Oral	106 (64)	98 (59)	—
Transdermal	59 (36)	67 (41)	—
Duration of estradiol replacement (d)	24.1 ± 7.9	24.9 ± 8.5	.37[b]
Endometrial thickness on transfer day (mm)	9.3 ± 1.9	9.7 ± 2.1	.044[b]
Donor age (y)	26.4 ± 4.5	26.1 ± 4.6	.58[b]
Received cumulus-oocyte complexes	7.3 ± 2.2	7.3 ± 2.0	.96[b]
Mature (MII) oocytes	5.8 ± 1.3	5.9 ± 1.2	.42[b]
Fertilized oocytes (2PN)	4.5 ± 1.4	4.7 ± 1.4	.16[b]
Proportion of day 2/3 embryo transfers			1.0[a]
Day 2 embryo transfer, n (%)	78 (47)	78 (47)	—
Day 3 embryo transfer, n (%)	87 (53)	87 (53)	—
Summed combined embryo score	8.2 ± 1.3	8.2 ± 1.2	.85[b]
Overall pregnancy rate	102/165 (61.8)	96/164 (58.5)	.76[a]
Clinical pregnancy rate	84/165 (50.9)	81/164 (49.4)	.87[a]
Implantation rate[c]	114/330 (34.5)	103/328 (31.4)	.54[a]
Twinning rate[c]	29/84 (34.5)	21/81 (25.9)	.38[a]
Ongoing pregnancy rate	71/165 (43)	70/164 (42.7)	.96[a]
Extrauterine pregnancy rate	0/165 (0)	1/164 (0.6)	.31[a]
Biochemical pregnancy loss rate	18/102 (17.6)	15/96 (15.6)	.75[a]
Miscarriage rate	13/84 (15.5)	11/81 (13.6)	.76[a]

Note: Values are mean ± standard deviation.
[a] Chi-square test.
[b] Independent *t*-test.
[c] As detected with a transvaginal ultrasound at 7th pregnancy week.

Bodri. Transvaginal ultrasound-guided ET. Fertil Steril 2011.

our trial the speculum was removed before inserting the probe with the aim of obtaining a potentially better ultrasound image.

A main strength of our study is that a very homogeneous donor oocyte recipient population was used, devoid of the important confounding factors that have been inevitably present in many other infertility trials. There are only a handful of known prognostic factors that could have an important impact on the outcome of oocyte donation cycles (uterine anomalies, black race, Turner syndrome, and the number and developmental stage of transferred embryos) and these were controlled for in the present trial. The study's weaknesses were related to the fact that the chosen equivalence margin was fairly large (±15%) and that randomization was not stratified according to the two different operators performing the procedures. Moreover, the operators and patients were not blinded (necessarily so) to the different techniques used, so unknown confounding factors (such as performance bias) might have influenced the trial results.

Our randomized clinical trial found no statistically significant difference in pregnancy rates comparing the TV versus the TA ultrasound-guided ET procedure. The TV approach is associated with increased patient comfort due to the absence of bladder distension. Further studies are needed to define the patient groups in whom the TV approach might be superior to the currently more widely used TA ultrasound guidance.

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SUPPLEMENTAL MATERIALS AND METHODS

Ultrasound Equipment, before and after Transfer Events

All patients were asked to come to the clinic with a full bladder without receiving any premedication. The patients who were randomized to transvaginal (TV) ultrasound guidance were asked to void their bladder immediately before the procedure. Portable ultrasound equipment (Sono Site Micromaxx, Sonosite Ibérica S.L.U., Las Rozas de Madrid, Spain) was used with 8–5 MHz vaginal and 5–2 MHz abdominal transducers, respectively. The vaginal probe was covered with a sterile cover during embryo transfer (ET) and thoroughly cleaned between procedures. Immediately after the procedure patients in the transabdominal (TA) arm were permitted to void their bladder by getting up and going to the toilet. All patients remained 30 minutes in a reclined position in a private room before returning home. Instructions for after the ET encouraged a normal lifestyle with the avoidance of intense physical exercise.

Transabdominal Ultrasound-Guided ET

The TA ultrasound-guided ET is the center's standard approach and was performed as follows. The physician inserted a sterile Collin vaginal speculum; the cervix was exposed and gently cleansed with sterile gauze pads. Cervical mucus was gently removed with a syringe if abundant. The transfer procedure was performed using a two-stage technique ("afterloading") in close collaboration with the embryologist. The TA ultrasound scan was concomitantly performed by a trained nurse. The Sure View Wallace Embryo Replacement Catheter (No. CE118; Smith Medical, Hythe, Kent, UK) is composed of a Teflon, 18 cm-long, straight, outer sheath and a 23-cm-long, soft echogenic (due to embedded small air bubbles) inner catheter.

First, only the outer sheath was inserted into the cervix until reaching the internal cervical os. If the negotiation of the cervical canal was not achieved, a similar outer sheath obturated with a rigid malleable stylet was used (No. 1816ST). After verifying the catheter's position on the TA ultrasound scan, the physician gave the signal to the embryologist to start the embryo loading. The embryologist was located within 2 meters of the physician in the adjacent part of the embryology laboratory, separated by a swinging door. Two selected embryos were loaded into an echogenic inner soft catheter between two small air bubbles using Uterine Transfer Medium (Medicult, Jyllinge, Denmark). When finished, the embryologist brought the loaded inner catheter and inserted it into the outer sheath, which was maintained in its position by the physician.

Afterward, under continuous ultrasound control, the inner echogenic catheter was advanced within a 10 to 20 mm distance of the uterine fundus by the physician. Finally, at the physician's signal, approximately 0.3 μL of media volume was injected by the embryologist, and the appearance of echogenic spot(s) generated by air bubble(s) was observed on the scan. After 10 seconds, the inner catheter was slowly removed. Any retained embryos were immediately retransferred using the same technique.

Secondary Outcome Measures and Patient Questionnaire

The duration of the ET was measured by the study monitor and consisted of three partial times: catheterization time (the interval from the start of the catheter introduction into the cervix until its position was satisfactorily verified on ultrasound scan), embryo loading time (from the start of embryo loading until the inner catheter was inserted into the outer sheath), and injection time (the time needed for the advancement of the inner catheter until the injection of the droplet containing the embryos). The difficulty of the ET was defined as "without any difficulty" (smooth introduction of the catheter and prompt injection of the embryos), "with moderate difficulty" (longer, more difficult, or repeated introduction of the catheter), or "highly difficult" (e.g., use of a cervical dilatator or reconversion of the intended technique).

Uterine cramping and discomfort/pain related to bladder distension were evaluated by a patient questionnaire administered immediately after the ET procedure. The patient questionnaire consisted of three simple questions: [1] During the embryonic transfer, did you experience uterine cramps or pain similar to menstrual pain? *Answers*: None, minor, moderate, or strong. [2] During the embryonic transfer, did you experience discomfort caused by having a full bladder, or emptying it? *Answers*: None, minor, moderate, or strong. [3] How would you evaluate your comfort during the procedure as a whole? *Answers:* No discomfort, minor discomfort, moderate discomfort, or strong discomfort.