Cervical dilatation has a positive impact on the outcome of IVF in randomly assigned cases having two previous difficult embryo transfers

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BACKGROUND: The difficulty of embryo transfer has been reported to affect success rates in some centres, but not in others. Cervical dilatation has been proposed as a means to overcome difficult embryo transfer, but consistent criteria for patient selection are lacking. In a prospective randomized study, we examined the influence of cervical dilatation 1–3 months before embryo transfer on the outcome of IVF in cases having difficult embryo transfer in two previously failed IVF cycles. METHODS: Two alternative methods of embryo transfer preparation were evaluated in 283 randomly assigned women having difficult embryo transfers in two previously failed IVF attempts. Randomization was made using a computer-generated random number table. Cervical dilatation before starting any IVF treatment was used in 145 cases, and no dilatation was performed in 138 cases. RESULTS: The cervical dilatation group yielded a significantly higher pregnancy rate than the non-dilated group (40% versus 24%; P < 0.01). Likewise, the implantation rate (24.1% versus 14.9%; P < 0.01) and the live birth rate (34.48% versus 19.56%; P < 0.01) were significantly higher in the dilatation group than in the non-dilated group.

CONCLUSIONS: In patients with prior difficult embryo transfer, cervical dilatation 1–3 months before embryo transfer lead to an improved pregnancy rate.

Key words: cervical dilatation/cervical stenosis/embryo transfer/IVF/transfer catheter

Introduction
The success of an IVF cycle is dependent on many factors, several of which are influenced not only by the patient, but also by the skill of the treating physician. Although implantation is poorly understood in humans, the pregnancy rate following embryo transfer is affected by several known variables, such as embryo quality (Scott et al., 1991), number of previous attempts and presence of blood or mucus on the transfer catheter (Nabi et al., 1997), age of the patient, number of embryos transferred, cause of infertility (Rooseboom et al., 1995), uterine receptivity (Prapas et al., 1998b) and the presence of uterine contractions (Fanchin et al., 1998). Furthermore, catheter choice (Gonen et al., 1991) or use of ultrasonography-guided transfer (Prapas et al., 1995; Woolcott and Stranger, 1997; Wood et al., 2000) have been reported to affect success rates in some centers, but not others (Al-Shawaf et al., 1993; Nabi et al., 1997; Kan et al., 1999). Likewise, some studies report that difficulty of embryo transfer is not detrimental to pregnancy outcome (Broussin et al., 1998; Tur-Kaspa et al., 1998).

Reports that difficult transfers and the provider performing the embryo transfer may negatively affect the success rate (Leeton et al., 1982; Groutz et al., 1997; Nabi et al., 1997; Hearns-Stokes et al., 2000; Spandorfer et al., 2003) raise concern that ‘easy’ embryo transfer may be a major determinant of a successful transfer. Furthermore, it was suggested that during embryo transfer, excessive movement of the catheter tip may lead to endometrial trauma (Woolcott and Stranger, 1997; Letterie et al., 1999) or transcervical embryo expulsion (Ghazzawi et al., 1999).

Cervical dilatation has been proposed as a means to overcome difficult embryo transfer in patients with cervical stenosis (Abusheikha et al., 1999; Serhal et al., 2003). However, neither the therapeutic effect nor the optimal timing (before or after the stimulation phase of the IVF cycle) of this procedure is clear. In addition, consistent criteria to decide which patient needs cervical dilatation are non-existent.

The present study is a prospective randomized trial to evaluate the value of cervical dilatation in cases of ‘difficult’ embryo transfer in previously failed IVF attempts.

Materials and methods
This study was based on a 2-year survey (March 2000 to March 2002) of two different embryo transfer preparations for women having a ‘difficult’ embryo transfer in two previously failed IVF attempts.
The embryo transfer was undertaken using the Wallace embryo replacement catheter (SIMS Portex Ltd, Hythe, UK) under ultrasound control. The preloaded Wallace catheter was passed immediately through the cervix into the middle of the uterine cavity as described by Zech et al., (1997). The stiffer outer sheath of this catheter remained in the cervical canal and was not used to force the thin catheter into the uterus in any way. When difficulty was encountered, the hard Wallace malleable stylet was used to facilitate the catheter entry. If difficulty was encountered while introducing the hard Wallace malleable stylet the patient was considered to have 'difficult' embryo transfer.

Data were prospectively collected for 283 women [145 having cervical dilatation (group I) and 138 without cervical dilatation (group II)] participating in the IAKENTRO ART Program from March 2000 to March 2002. The total number of IVF cycles performed at the same period in our center was 2116 cycles, giving a pregnancy rate of 32.48% per transfer, while transfers classed as ‘difficult’ occurred in 392 (18.5%) of cycles. One case from group I in which the uterus was perforated (0.68%) and four cases from group II with cancelled stimulation (2.81%) were eliminated from the statistical analysis because no embryo transfer was conducted. Admission of a patient to the study depended on additional strict criteria: all patients >42 years of age, or with FSH levels >15 IU/ml on cycle day 3 or hyperstimulated (estradiol >2500 pg/ml) or presenting hydrosalpinx were excluded from the study. Subjects were randomized into group I (cervical dilatation) or group II (no cervical dilatation) by an allocation sequence generated from a computerized random number table.

Cervical dilatation to Hegar number 9 was performed under general anesthesia 1–3 months before starting any IVF treatment. Pituitary down-regulation was achieved by administering the GnRH agonist triptorelin (0.1 mg subcutaneously) in a long stimulation protocol (Prapas et al., 2001). Multiple follicle development was induced with 225–300 IU/day of recombinant human FSH (Gonal-f, Serono Pharmaceuticals; Puregon, Organon) or highly purified urinary FSH (Metrodin; Serono Pharmaceuticals). The criterion for use of recombinant FSH was the patient’s insurance financial coverage. A single injection of 10 000 IU of HCG (Profasi, Serono Pharmaceuticals; Pregnyl, Organon) was administered to induce the final stage of oocyte maturation, and transvaginal, ultrasound-guided follicular aspiration was performed 34–36 h later.

Study design

To qualify for inclusion in the study, at least one good quality embryo in relation to the day of embryo transfer was needed. Classification of embryos was based on either the number of blastomeres or the developmental stage. In determining which embryos were suitable for day 3 transfer, parameters such as fragmentation and equality of blastomeres were taken into consideration (Veeck, 1998). embryo transfer after 3 days of culture usually occurs at the 6- to 8-cell stage of embryonic development. Embryos that did not reach the 6-cell stage after 3 days of culture were considered developmentally retarded. For statistical reasons we quantified the scoring system of Veeck (1998) as follows: on day 3, embryos presenting 6–7 cells were given 1 point, 8–10 cells 2 points and embryos in compaction process 3 points. Additionally, we added 3 points for the A quality embryos, 2 points for the B and 1 point for the C. All women undergoing replacement of embryos had a maximum of three embryos transferred.

Progestosterone supplementation was given, beginning on the day of oocyte retrieval. The laboratory techniques and the culture media have been described previously (Vanderzwalmen et al., 1996; Gardner et al., 1998).

Technique of embryo transfer

Embryo replacement was carried out 3 days after oocyte retrieval. All our embryo transfers were performed under ultrasound control with full bladder (Prapas et al., 1995). The Wallace embryo replacement catheter (SIMS Portex Ltd) was used in all cases and embryos were deposited in the middle of the uterine cavity as described elsewhere (Zech et al., 1997).

Statistical analysis

Student’s t-test was used in order to detect any statistically significant differences between the two groups (cervical dilatation and no dilatation) with respect to the number of embryos transferred, the mean quality of embryos (quantified using the scoring system of Veek), the mean number of oocytes retrieved and fertilized, and the age of the subject, on embryo transfer day 3. A P-value <0.05 was considered statistically significant.

The χ²-test and Fisher’s exact test were used to test the hypothesis of equal pregnancy rates in the cervical dilatation and no dilatation groups.

Results

A total of 288 women with two previous ‘difficult’ embryo transfers were enrolled in the study. One hundred and forty-six women were randomly allocated to group I (dilatation) and 142 were allocated to group II (no dilatation). A flow chart of inclusion, randomization and drop-out of patients treated in the study is shown in Figure 1.

The mean age of patients and the mean number and quality of embryos replaced in the compared groups are summarized in Table I. The mean number of embryos transferred and the embryo quality, as assessed by the scoring system of Veek (1998), was similar in the compared groups, as were the mean values of other indications (oocytes retrieved and fertilized). Ninety-one clinical pregnancies were achieved, corresponding to an overall success rate of 32.15% per embryo transfer. embryo transfer in group I resulted in 58 pregnancies (40%), and in group II resulted in 33 pregnancies
Cervical dilatation in patients with previously difficult ETs

The impact of difficult embryo transfer on pregnancy rates is a subject of debate in the literature. Some studies have shown that there is a correlation between difficult embryo transfer and a reduced pregnancy rate (Marcus et al., 1993; Spandorfer et al., 2003), whereas others have suggested that difficult or repeated embryo transfer does not adversely affect outcome (Broussin et al., 1998; Tur-Kaspa et al., 1998). These contradictory findings may be explained in several ways. Most series of patients studied have been relatively small. Furthermore, different definitions of ‘difficult’ embryo transfer, which is a subjective diagnosis, have been used and patient selection has not been uniform. Variables that can and have been used include transfer catheter type (Gonen et al., 1991), difficulty of transfer (Mansour et al., 1990), number of attempts, and presence of mucus and blood on the transfer catheter (Nabi et al., 1997).

In view of this proposed detrimental effect of difficult embryo transfer on pregnancy and implantation rates, different maneuvers have been practiced to predict and prevent technical difficulties at embryo transfer. These include the performance of a dummy or mock embryo transfer before the actual embryo transfer (Mansour et al., 1990; Knutzen et al., 1992), the use of a full bladder or a tenaculum to straighten the uterine axis (Sundstrom et al., 1984; Sharif et al., 1995), and the use of ultrasonographic guidance at the time of embryo transfer (Prapas et al., 1993). All these practices are useful, but a subset of patients remains in whom embryo transfer is still difficult or impossible. In these patients, difficulty in passing an embryo transfer catheter usually is encountered at the level of the internal os. Dilatation of the cervical os therefore is the logical step to overcome difficult embryo transfer in these women.

In this present prospective randomized study, the use of the Wallace malleable stylet in two previous failed IVF attempt was seen as a consistent criterion for grading embryo transfer as ‘difficult’ as opposed to ‘easy’. Our study showed that in patients with prior ‘difficult’ embryo transfer, cervical dilatation significantly improved the pregnancy rate of IVF. As a result, correct timing (Prapas et al., 2001), receptivity of the uterus (Prapas et al., 1998a), instrumentation (Schoolcraft et al., 2001) and presence of cervical stenosis (Mansour and Aboulghar, 2002) have been investigated by different groups, but no agreement exists as to the importance of each of these variables in the success of IVF.

### Table I. Clinical data of 283 IVF cycles according to the preparation for transfer

<table>
<thead>
<tr>
<th>Group I: cervical dilatation (n = 145)</th>
<th>Group II: no dilatation (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients (years) 33.16 ± 4.5</td>
<td>32.48 ± 4.38</td>
</tr>
<tr>
<td>Mean number of oocytes retrieved 9.05 ± 4.61</td>
<td>9.24 ± 4.42</td>
</tr>
<tr>
<td>Mean number of oocytes fertilized 5.36 ± 2.69</td>
<td>5.44 ± 2.54</td>
</tr>
<tr>
<td>Mean number of embryos transferred 2.24 ± 1.02</td>
<td>2.41 ± 1.27</td>
</tr>
<tr>
<td>Embryonic score 4.54 ± 0.83</td>
<td>4.53 ± 0.75</td>
</tr>
</tbody>
</table>

All differences between the two groups are non-significant. Data are mean ± SD.

(23.91%) (P < 0.01). Likewise, the implantation rate differed significantly (P < 0.01) between the compared groups (Table II). In six cases in group I the embryo transfer remained difficult (4.13%). Six pregnancies from the dilatation group and five from the no dilatation group resulted in first trimester abortions. Two women at 23 weeks and one at 22 weeks of gestation from group I (2.06%) not in labour presented dilated cervix (4–9 cm) and the fetal membranes bulging through the cervix. Two of them experienced fetal loss while the third had 4 cm cervical dilatation at 23 weeks of gestation after an urgent cerclage and bed rest, and delivered at the beginning of the 28th week of gestation. All these women had multiple pregnancies. Additionally, three women in the cervical dilatation group (2.06%) and two in the non-dilatation group (1.44%), during the routine transvaginal ultrasound control of the cervix between 20th and 24th week of gestation, were diagnosed with cervical length <2.5 cm. In all these cases a preventive cervical cerclage was placed. All these women had multiple pregnancies and delivered at term.

The live birth rate was statistically significantly higher in the cervical dilatation group 34.48% compared with the non-dilatation group 19.56% (P < 0.01). The first and the second trimester abortions, as well as the preterm live deliveries rates, were not statistically different between the two groups (Table II).

### Discussion

The embryo transfer procedure is performed at least partially blindly and seems to contribute to the high failure rate of IVF. As a result, correct timing (Prapas et al., 2001), receptivity of the uterus (Prapas et al., 1998a), instrumentation (Schoolcraft et al., 2001) and presence of cervical stenosis (Mansour and Aboulghar, 2002) have been investigated by different groups, but no agreement exists as to the importance of each of these variables in the success of IVF.

Table II. Obstetric outcome in 283 women participating in the study

<table>
<thead>
<tr>
<th></th>
<th>Group I: cervical dilatation (n = 145), % per transfer</th>
<th>Group II: no dilatation (n = 138), % per transfer</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pregnancies</td>
<td>58 (40%)</td>
<td>33 (23.91%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Implantation rate</td>
<td>24.1%</td>
<td>14.9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>1st trimester abortion</td>
<td>6 (4.13%)</td>
<td>5 (3.62%)</td>
<td>NS</td>
</tr>
<tr>
<td>2nd trimester abortion</td>
<td>2 (1.37%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Live deliveries, all gestations</td>
<td>50 (34.48%)</td>
<td>27 (19.56%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Preterm</td>
<td>6 (4.13%)</td>
<td>3 (2.17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Term</td>
<td>44 (30.34%)</td>
<td>24 (17.39%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NS = not significant.
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(dilatation 40% versus no dilatation 23.91%; P < 0.01) and the live birth rate (34.48% versus 19.56%; P < 0.01).

The timing of cervical dilatation is still debatable. Cervical dilatation during ovum pick-up has been reported to affect success rates in some centres (Visser et al., 1993; Groutz et al., 1997), but not others (Broussin et al., 1998). Abusheikha et al. (1999) performed cervical dilatation on the day of the initial visit either during or immediately after the patient’s menstruation and the embryo transfer was performed 2 weeks later. After cervical dilatation they reported a higher pregnancy rate in the easy embryo transfer group compared with the difficult embryo transfer group (40% versus 11.8%). In our study, the cervical dilatation was performed any time before starting IVF treatment (1–3 months), thus the embryo transfer was performed at least 28 days after the dilatation. We have postulated that a period of time between cervical dilatation and embryo transfer is needed for any cervical and endometrial trauma to heal and to minimize the risk of expulsion of the embryos from the uterine cavity due to delayed uterine contractions (Ghazzawi et al., 1999).

Abusheikha et al. (1999) reported that cervical dilatation to Hegar number 7 significantly increased the ease of transfer in 70.2% of patients with known cervical stenosis, while Serhal et al. (2003), by using hygroscopic rods prior to ovarian stimulation, increased the percentage of easy embryo transfer to 79.6%. By performing cervical dilatation to Hegar number 9 we changed 95.86% (139 out of 145) of difficult embryo transfers into technically easy transfers.

One possible objection to the use of cervical dilatation might be the risk of cervical incompetence and uterine perforation. In the beginning of our study, in one case the uterus was perforated during the cervical dilatation. Since then we perform the cervical dilatation under ultrasound control to eliminate the risk of uterine perforation. The cause of cervical incompetence is obscure, and a variety of aetiological factors have been proposed, one of which is the trauma to the cervix in the course of a dilatation (Golan et al., 1989). Clinically diagnosed cervical incompetence resulted in three out of 145 of our cases in the dilatation group (2.06%) and none in the non-dilatation group. All these women had multiple gestation. The use of transvaginal ultrasound assessment (TVS) during the pregnancy was proposed as first choice in any high-risk pregnancy for cervical incompetence (Maymon et al., 2001). Additionally, the preventive use of cervical cerclage and the bed rest was suggested to reduce the risk of preterm delivery in women at high risk for cervical incompetence such as women presenting cervical length <2.5 cm before the 27th week of gestation during a transvaginal ultrasound assessment (Althuisius et al., 2002). In our study, the percentage of women presenting cervical length <2.5 cm before the 24th week of gestation was not different between the two groups (2.06% versus 1.44%). Obviously, we were not able to conclude whether the cervical incompetence or the shortening of the cervical length presented in some of our cases with multiple pregnancy was due to the cervical dilatation or the multiple pregnancy, or to other factors involved, since the differences between the groups compared were not statistically significant. Nevertheless, repeated TVS cervical assessment between the 20th and 24th weeks of pregnancy is advised to be performed in any IVF case presenting multiple pregnancy that previously had cervical dilatation.

We conclude that cervical dilatation to Hegar number 9 before starting any IVF treatment in patients who have previously had a difficult embryo transfer using the Wallace malleable stylet allows a technically easier embryo transfer, and helps to achieve a higher pregnancy rate.

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