The impact of the embryo transfer catheter on the pregnancy rate in IVF

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BACKGROUND: The aim was to assess whether the type of embryo transfer set used for embryo transfer affects the ongoing pregnancy rate in IVF. METHODS: The TDT set was compared with the K-soft 5000 in a large, prospective, randomized study. Patients were randomized moments before transfer by drawing a consecutively numbered, sealed, opaque envelope indicating the catheter to be used. RESULTS: 2059 embryo transfers in 1296 patients were analysed. The ongoing pregnancy rate was significantly higher in the K-soft group. If the first transfer of a patient (n = 1296) within this study period was analysed, the ongoing pregnancy rates were 27.1 versus 20.5% (P = 0.006). If the analysis is limited to patients that underwent their very first transfer ever (n = 607), the ongoing pregnancy rates were 30.3 versus 20.0% (P = 0.003) in favour of the K-soft. CONCLUSION: We conclude from these data that the type of embryo transfer set used for embryo transfer does affect the ongoing pregnancy rate and that the impact of the variable transfer catheter on the ongoing pregnancy rate increases when the a priori chance of pregnancy increases.

Key words: catheter/embryo transfer/IVF/pregnancy rate/transfer procedure

Introduction

The final step in the IVF treatment is the embryo transfer, a procedure which has not changed dramatically since the introduction of IVF in 1978. However, various factors concerning embryo transfer that might affect the chance for an ongoing pregnancy have been identified, such as the experience of the physician (Lu, 1999), the use of ultrasound guidance (Kan et al., 1999; Coroleu et al., 2000; Rijnders et al., 2000), the ease of the procedure (Lesny et al., 1998), the presence or absence of blood on the catheter (Goudas et al., 1998), bacterial contamination of the catheter (Ègbase et al., 1999) and the type of catheter used for the transfer (Gonen et al., 1991; Perin et al., 1997; Meriano et al., 2000).

The impact of these factors has been investigated in relatively small samples, although the examination of a single factor in reproductive medicine is more reliable when large groups are involved (Templeton et al., 1996; Ramsay, 1999). In order to optimize each single step of the IVF treatment in our centre, we analysed the factor ‘embryo transfer catheter’ in a large group. In previous studies comparing embryo transfer catheters, the number of transfers was relatively small; Gonen et al. compared 193 transfers retrospectively (Gonen et al., 1991), Perin et al. compared 248 transfers prospectively (Perin et al., 1997), and Meriano et al. compared 66 transfers prospectively (Meriano et al., 2000). Therefore, a large, prospective, randomized, transfer-orientated, comparative study was designed. The aim of this study is to test the hypothesis that the ongoing pregnancy rate is affected by the type of catheter used for the embryo transfer procedure.

Commercially available embryo transfer catheters can be subdivided by the material they are made of (i.e. metal, hard plastics, or soft plastics) and whether they are equipped with or without an introducing cannula that facilitates the transfer procedure. At the VU university medical centre, two cannula equipped embryo transfer catheter sets are in use for embryo transfer: the TDT set (Laboratoire CCD®, Paris, France) and the Cook K-soft 5000 ‘soft trans universal’ set (Cook® IVF, Eight Mile Plains, Queensland, Australia). These embryo transfer sets are compared in this study. There are no vested interests of commercial nature between the authors, the IVF centre of the VU University Medical Centre and the manufacturer of either embryo transfer catheters.

Materials and methods

This prospective, randomized, comparative study was conducted according to the rules of the Institutional Review Board of the VU University Medical Centre.

The ongoing pregnancy rate, in the years when the TDT set was used solely as transfer catheter, was ~18% per embryo transfer. On the assumption that a higher ongoing pregnancy rate would be yielded by the K-soft 5000, we calculated that 1021 transfers were necessary...
in each arm to detect a difference of 5% in ongoing pregnancy rates between the two types. For this calculation, the expected pregnancy rate for the TDT was set at 18% and for the K-soft at 23%; this calculation provides the study with 80% power at the 5% significance level.

The women were randomized by drawing a sealed, consecutively numbered, opaque envelope containing a form indicating which catheter should be used for the transfer procedure. The envelopes were, prior to the study, randomized in blocks of 20 using a randomization table. This method made sure that after every 20 transfers, 10 transfers were allocated to the TDT group and 10 to the K-soft group.

Since the transfer catheter was the subject of investigation, the decision was made to include all patients eligible for embryo transfer. Exclusion criteria were transfer of cryopreserved embryos or participation in another study protocol.

Ovarian stimulation, oocyte retrieval, insemination technique, and embryo culture technique were performed as described elsewhere (Roseboom et al., 1995; Goverde et al., 2000).

Embryo transfer catheter sets

The TDT embryo transfer set consists of a single lumen 18 cm long polyethylene (Lotrène CD 0230 Norsolor, Paris, France) cannula (Frydman 4.5) and a partly polyethylene (Lotrène CD 0230, Norsolor), partly metal (Inox 302, Thiebaud, Thonon-les-Bains, France) transfer catheter. The cannula is standard equipped with a malleable metal (Inox 302, Thiebaud) obturator allowing to bend it into the required curve necessary for passage through the cervical canal. Two indicator lines on the cannula indicate the depth of insertion at 6 or 7 cm from the external os. After insertion of the cannula into the cervix, the malleable metal obturator is removed and the transfer catheter is loaded with the embryos and inserted into the cannula up to the indicator dot. The cannula is pulled back gently by ~2 cm. The tip of the catheter will lie freely in the uterine cavity and the embryos are expelled into the uterine cavity.

The Cook® K-soft 5000 soft trans universal embryo transfer set consists of a single lumen cannula with a 12.5 cm rigid proximal part and a 4.0 cm soft distal part. The transfer catheter is made of an undisclosed soft polyurethane material that is proven to be non-toxic in mouse embryo culture. The cannula is standard, not equipped with a metal obturator. A separate packed malleable obturator can be inserted into the cannula, making it possible to bend the cannula in a sharper angle for difficult passage of the cervical canal. After introduction of the cannula into the cervix up to the internal os, the transfer catheter is inserted via the cannula into the uterine cavity; indicator dots mark the depth of insertion at 4–7 cm from the external os. There is no need to retract the cannula before expelling the embryos.

Embryo selection and transfer procedure

Embryo transfer was performed on day 2, 3 or 5 after oocyte retrieval. Prior to the transfer procedure, the embryo development and morphology score were determined and the embryos were selected. Each embryo was scored according to its symmetry and the extent of fragmentation of blastomeres. Briefly, grade 1 embryos contained symmetrical and unfragmented blastomeres, grade 2 embryos were even but with slight cellular debris and grade 3 embryos had at least one degenerated cell.

In general, no more than two embryos were transferred. However, if the embryo quality was poor and the patient was >38 years of age and had had several previous implantation failures, the physician could suggest to transfer three embryos. Transfer on day 5 after oocyte retrieval was performed only if the patient had had at least two previous implantation failures or if a single embryo transfer was requested or indicated. No more than two embryos were transferred on day 5.

The transfer procedure itself was standardized as far as possible amongst the participating physicians to eliminate bias. All patients were placed in the lithotomy position and no anaesthetics or sedative drugs were used. After insertion of a sterile preheated Trélat speculum to expose the cervix, the exocervix was cleaned with a sterile swab and the endocervix was cleaned with a sterile Q-tip. The cannula was then introduced, passing the cervical canal. With the cannula in position, the embryologist was asked to load and present the transfer catheter to the physician. Embryos were drawn up into the transfer catheter with the aid of a disposable tuberculin syringe using the ‘three drop procedure’ in which the embryos are separated by a bubble of air from a preceding and a following drop of medium. The transfer catheter was inserted into the uterine cavity at a depth of 6 cm from the external os. The embryos were then gently expelled into the uterine cavity in a volume of 25–35 µl culture medium. The cannula and transfer catheter were flushed with medium under a stereomicroscope to ensure that the embryos were actually released into the uterine cavity. After the embryo transfer, the patients remained in a horizontal position for 15 min.

If introduction was impossible with the allocated catheter, the type of catheter was changed. The ease of introduction was scored subjectively by the physician as ‘easy’, ‘difficult’, ‘very difficult’, or ‘impossible with the allocated catheter’. If introduction with the K-soft catheter was not possible, the TDT was used and vice versa. When, in the case of transfer with the K-soft, the obturator was required, this was indicated on the sheet and the procedure was considered to be not easy and was recorded according to protocol as ‘difficult’ or ‘very difficult’. The presence or absence of blood was recorded as ‘no blood’, ‘blood on the cannula’, or ‘blood on the transfer catheter’.

Outcome

A pregnancy test was performed 14–16 days after follicle aspiration. Pregnancy was defined as serum HCG level ≥50 IU. An ongoing pregnancy was defined as an intrauterine pregnancy with fetal cardiac activity 70 days after follicle aspiration.

Analysis

All randomized patients were included in the comparison and the analysis was performed on an intention-to-treat basis. The data were analysed in three ways in relation to the patient group. (i) All embryo transfers were included, meaning that if a patient had more than one embryo transfer in the study, all the transfers during the study were included (embryo transfer-based analysis). (ii) Only the first embryo transfer within this study was included irrespective the number of previous transfers prior to the study period. Consecutive transfers within the study period were excluded (patient-based analysis). (iii) Only the first embryo transfer a patient ever underwent in her life as unit of analysis (first IVF cycle-based analysis).

Since the patient-based analysis provided sufficient statistical power to test the hypothesis, the decision was made to use only the second and the third analysis for this report. These groups are the purest from epidemiological point of view.

Statistical analysis

Statistical analysis was performed using SPSS for Windows release 9.0 (SPSS Inc., Chicago, IL, USA). Data were compared by the unpaired t-test or \( \chi^2 \) analysis, where applicable. The differences were considered significant at a level of \( P < 0.05 \).
Table I. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patient oriented</th>
<th>First IVF cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K-soft</td>
<td>TDT</td>
</tr>
<tr>
<td>n</td>
<td>639</td>
<td>657</td>
</tr>
<tr>
<td>Age</td>
<td>34.5 (4.14)</td>
<td>34.3 (4.13)</td>
</tr>
<tr>
<td>Primary (%)</td>
<td>64.0</td>
<td>63.0</td>
</tr>
<tr>
<td>Years infertile</td>
<td>4.5 (2.85)</td>
<td>4.4 (2.91)</td>
</tr>
<tr>
<td>IVF indication</td>
<td>Tubal pathology</td>
<td>31.9</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Male factor</td>
<td>41.9</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>ICSI (%)</td>
<td>34.4</td>
</tr>
<tr>
<td></td>
<td>No. of oocytes</td>
<td>10.5 (6.66)</td>
</tr>
<tr>
<td></td>
<td>Fertilization (%)</td>
<td>62.5 (23.4)</td>
</tr>
<tr>
<td></td>
<td>No. transferred</td>
<td>2.04 (0.41)</td>
</tr>
<tr>
<td></td>
<td>Day of transfer (%)</td>
<td>Day 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 5</td>
</tr>
</tbody>
</table>

Values are mean (SD) except where indicated.
There were no significant differences between catheter groups, in either set.

Results

Between September 1998 and February 2000, 2100 consecutive embryo transfers were randomized. Forty-one transfers were excluded from analysis: (i) because accidentally a frozen–thawed embryo transfer was included (33), (ii) accidentally the patient included was also included in another research programme or (iii) follow-up could not be completed. Finally, 2059 embryo transfers performed by 14 physicians in 1296 patients were available for analysis. In all, 607 patients had their first embryo transfer ever during the study period.

Baseline characteristics were similar in the two randomized groups and their subsets and are summarized in Table I. Embryo transfer characteristics concerning ease of introduction and blood are shown in Table II. Embryo quality was slightly better in the Cook ‘first IVF cycle’ group. The pregnancy rate between the various physicians was not statistically significantly different, nor were pregnancy rates in the K-soft group influenced by the use of the obturator (data not shown).

In those cases where the transfer with the allocated catheter was not possible, a successful transfer with the ‘other’ catheter was always achieved.

In the patient-oriented group, the ongoing pregnancy rate was 27.1% for the K-soft versus 20.5% for the TDT (P = 0.006); in the ‘first IVF group’, the ongoing pregnancy rate was 30.3% for the K-soft versus 20.0% for the TDT catheter (P = 0.003).

Discussion

The results of this study clearly indicate that the type of embryo transfer catheter contributes significantly to the success rate of an IVF programme. When we limit the analysis to one patient–one transfer, a stronger association between the ongoing pregnancy rate and the use of the K-soft transfer set occurs. Patients have the highest chance for a clinical pregnancy in their first IVF treatment (Templeton et al., 1996). When we limit the analysis to this group of patients, a substantial number of patients remains. It is in this particular group that the K-soft transfer set performs best.

This is by far the largest prospective, randomized study between two types of embryo transfer catheters ever conducted, complying with one group’s recommendations for investigation of a single factor in IVF (Templeton et al., 1996). Since embryo transfers in our centre are conducted by various clinicians, the danger of bias by inter-operator variability is present in this study (Hearns-Stokes et al., 2000). To avoid this bias, all clinicians in our centre were trained to transfer the embryos in an identical way into the lower uterine cavity (Waterstone et al., 1991). It has been shown that in this way the inter-individual differences between the clinicians almost completely disappear (Naaktgeboren et al., 1998). Both types of transfer set in this comparison were introduced, as instructed by the manufacturer, in such a way that the embryos are deposited at 6 cm from the external cervical ostium in order to avoid abutting the fundus of the uterus. Physical stimulation of the fundus can initiate uterine junctional zone contractions, and this mechanical activity can relocate the embryos and reduce the chance for pregnancy (Lesny et al., 1999).

Even though the transfer technique is basically simple, unexpected difficulties can be encountered during the transfer procedure, usually at the level of the internal cervical os. This can be caused by extreme flexion of the uterus or by stenosis of the cervical canal. A mock embryo transfer in a cycle prior to the actual IVF cycle is advocated to find the most suitable catheter for each patient in order to avoid such problems. The number of difficult transfers can be reduced in this way (Mansour et al., 1990; Knutzen et al., 1992; Sharif et al., 1995). Insertion of a cannula is in fact a mock transfer immediately prior to the real transfer, with the possibility of changing the type of embryo transfer set if necessary while...
the embryos remain in the incubator. In difficult cases is it
helpful when the cannula has certain rigidity and can be bent
in the anticipated curve.

For correct positioning of the TDT catheter: its cannula
must be introduced into the uterine cavity up to 6 cm from
the external cervical ostium, then the obturator must be
removed, after which the actual transfer catheter loaded with
the embryos can be inserted into the cannula; the cannula must
then be retracted by 2 cm before the embryos can be expelled
into the uterine cavity.

The K-soft cannula, on the other hand, is introduced until
it just passes the internal cervical ostium; the cannula itself
does not enter the uterine cavity. After positioning of the
cannula, the catheter is introduced and the embryos can be
expelled. If the cervical canal is in extreme
exposure or passage
is fixed
in the anticipated curve.

Both variables have a similar effect on the pregnancy rate in both catheter types. There is no
interaction between these variables and the catheter types for the chance of pregnancy.

Table II. Embryo transfer characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patient-oriented</th>
<th>First IVF cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K-soft</td>
<td>TDT</td>
</tr>
<tr>
<td>Ease of introduction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>78.3</td>
<td>94.6</td>
</tr>
<tr>
<td>Difficult</td>
<td>17.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Very difficult</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Impossible</td>
<td>3.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Blood (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>62.2</td>
<td>56.2</td>
</tr>
<tr>
<td>Catheter</td>
<td>6.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Cannula</td>
<td>22.7</td>
<td>29.5</td>
</tr>
<tr>
<td>Both</td>
<td>8.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Day 2 or 3ª</td>
<td>6.9 (2.35)</td>
<td>6.7 (2.19)</td>
</tr>
<tr>
<td>No. of blastomeres</td>
<td>1.8 (0.60)</td>
<td>1.8 (0.60)</td>
</tr>
<tr>
<td>Embryo quality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 5</td>
<td>86.8</td>
<td>84.4</td>
</tr>
</tbody>
</table>

ªValues are mean (SD).
Statistically significant differences are found within the catheter groups for the factors ‘ease of introduction’
and ‘blood’. Both variables have a similar effect on the pregnancy rate in both catheter types. There is no
interaction between these variables and the catheter types for the chance of pregnancy.

TDT transfer set. This is probably due to two reasons: first,
the TDT set is standard, equipped with a malleable obturator;
second, the study design. When designing the study we agreed
that, if the separate packed obturator for the K-soft was
requested, the transfer was to be ranked as difficult. This is
often true but not always, meaning that the number of difficult
transfers is overestimated in the K-soft group. Introducing the
K-soft cannula with the obturator is usually easy. It is therefore
not justifiable to conclude that the K-soft catheter is in general
more difficult to introduce. However, in 31 (3%) of the
transfers allocated to the K-soft, it was not possible to introduce
the K-soft cannula at all, while this was the case only three
times (0.3%) in the TDT group, a rate 10-fold lower than with
the K-soft catheter. It does seem therefore justifiable to state
that the TDT catheter succeeds more often if introduction is
ranked as ‘very difficult’ or (almost) impossible. Our observa-
tion that introduction of the TDT is usually easy is consistent
with the conclusions from other authors (Meriano et al., 2000).

Amongst clinicians, the absence of blood on the catheter or
cannula is ranked high as an important factor towards success
(Kovacs, 1999). This opinion is supported by literature reports
in which the presence of blood on the transfer catheter has
been associated with lower pregnancy rates (Visser et al.,
1993; Goudas et al., 1998). Yet, the variable blood has a
similar effect on the pregnancy rate in both transfer sets; hence
there is no interaction between the presence of blood on the
transfer set and the type of transfer set for the chance of
pregnancy. This means that the better results yielded by the
K-soft cannot be explained by the significantly smaller number
of blood stained transfer sets.

Another explanation for the difference in pregnancy rates
is the materials used for manufacturing the catheters. The
softer the materials used, the lesser the chance for damage
to the endometrium and the lesser the chance for uterine
contractions. The soft material of the K-soft embryo transfer set might be an explanation for the better results.

In conclusion, this study shows clearly that a relatively simple instrument like the embryo transfer catheter affects the chance for successful IVF outcome. The contribution of the factor transfer catheter on the outcome of the IVF treatment increases in a subgroup with a high a-priori chance of success. As the demand for reduction of the number of twin pregnancies by means of single embryo transfer (Strandell et al., 2000) increases, the type of embryo transfer catheter used for the embryo transfer must be chosen carefully.

References


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