A prospective, randomized, cross-over comparison of two methods of artificial insemination by donor on the incidence of conception: intracervical insemination by straw versus cervical cap

Paul A.Flierman1, Hendrikus V.Hogerzeil2 and Douwe J.Hemrika1,3

1Division of Reproductive Endocrinology and Fertility, Department of Obstetrics and Gynaecology, O.L. Vrouwe Gasthuis, Amsterdam and 2Division of Reproductive Endocrinology and Fertility, Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands

In a prospective, randomized study of insemination with donor semen, intracervical insemination by straw was compared with insemination using a cervical cap with an intracervical reservoir. A total of 91 patients completed 486 treatment cycles. There were no significant differences in age, parity, indication for insemination by donor, or method of cycle monitoring between women who became pregnant and those who did not conceive with either insemination method. In 236 standard intracervical insemination cycles, 14 patients became pregnant (5.9% per cycle), whereas 38 patients conceived in 250 cervical cap cycles (15.2% per cycle). Both the crude pregnancy rates and the cumulative pregnancy rates calculated by the Kaplan–Meier life-table method were significantly different ($\chi^2$-test, $P < 0.001$, and log-rank test, $P < 0.005$ respectively). Pregnancy rates in artificial insemination with cryopreserved donor semen may be improved by the use of a cervical cap when compared to cervical insemination by straw. The use of the cervical cap may prolong the exposure of the spermatozoa to the cervical mucus and prevent the backflow of semen into the vagina.

Key words: cervical cap insemination/conception/donor insemination

Introduction

Since the introduction of intracytoplasmic sperm injection (ICSI), artificial insemination with donor semen (AID) is no longer the primary choice of treatment in severe male factor infertility. Some couples, however, still resort to AID either because they object to the invasive and manipulative character of assisted reproductive technology or through fear of the hitherto unknown genetic risks involved in ICSI. In addition, when a pregnancy is not established after a number of treatment cycles of ICSI, couples may still want to proceed to AID as a second line of treatment.

The effectiveness of AID has been much debated since the abrupt switch around 1986 from the use of fresh semen to the exclusive use of cryopreserved semen to prevent the transmission of sexually communicable diseases [American Fertility Society (AFS), 1988]. While several authors reported lower conception rates for frozen versus fresh semen (Schoysman-DeBoeck and Schoysman, 1980; Richter et al., 1984; Barwin 1986), others found no significant differences (Bordsen et al., 1986; Keel et al., 1989). Nevertheless, since the discriminative parameter is the time necessary to achieve conception (rather than the mere cumulative pregnancy rate), it appears that, with fresh semen, fewer cycles are needed to achieve pregnancy (Steinberger et al., 1980).

In order to improve cycle fecundity when using cryopreserved donor semen, several studies compared the intra- or pericervical with the intrauterine route of insemination. From the results of these studies it seems that intrauterine insemination (IUI) is superior to intracervical insemination (Byrd et al., 1990; Patton et al., 1992; Wainer et al., 1995; Matorras et al., 1996), although one rather small study in single unmarried women failed to demonstrate a significant difference between the two techniques (Peters et al., 1993).

The advantage of a higher cycle fecundity with IUI has to be measured against the disadvantage of considerably higher costs per insemination cycle: IUI requires in-vitro sperm processing and is performed by the medical staff, whereas, in our institution, intracervical inseminations are performed by fertility nurses. Moreover, the semen preparation for IUI requires on average more donor semen for a single insemination than does intracervical insemination. This is especially relevant in our country where donor semen is a scarce commodity due to impending legislation that does not guarantee absolute future anonymity to the semen donor. Although we appreciate the value of IUI in AID, the above-mentioned drawbacks have prompted us to start treatment with simple, intracervical insemination.

In an attempt to optimize pregnancy rates per cycle with intracervical insemination, we have begun a prospective study to compare our conventional insemination technique, whereby a sperm reservoir is placed into the cervical longe the primary choice of treatment in severe male factor infertility. Some couples, however, still resort to AID either because they object to the invasive and manipulative character of assisted reproductive technology or through fear of the hitherto unknown genetic risks involved in ICSI. In addition, when a pregnancy is not established after a number of treatment cycles of ICSI, couples may still want to proceed to AID as a second line of treatment.

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In an attempt to optimize pregnancy rates per cycle with intracervical insemination, we have begun a prospective study to compare our conventional insemination technique, whereby the content of one 0.25 ml semen straw is deposited in the intracervical canal, with insemination by means of a cervical cap, whereby a sperm reservoir is placed into the cervical canal. Every patient was alternately treated with both methods.

Materials and methods

All patients with severe male factor infertility applying for AID treatment between January 1, 1991 and December 31, 1993 were asked to participate in the study. All patients gave their informed consent after appropriate counselling by the main investigator (D.J.H.). The study protocol was approved by the local hospital committee for The Ethics on Research Involving Human Subjects. In all female
The straws were allowed to thaw at room temperature for ~5 min. To examine the possible confounding effect of cycle monitoring, Chlamydia trachomatis each insemination. The quality and quantity of the cervical mucus was recorded at Three life-tables were constructed to facilitate comparison rates between the two groups was significantly different (LH) kit (Conceive, Quidel, San Diego, CA, USA): inseminations were performed both on the day of the urinary LH surge and the day 9.96,

By contrast, subjects inseminated with the cervical cap were allowed patients were inseminated according to the study protocol. Patient characteristics are given in Table I. Four patients with anovul-

The end-point of the study was defined either as pregnant [positive urinary human chorionic gonadotrophin (HCG) test; QuickView, Quidel, San Diego, CA, USA], as not pregnant after 12 completed cycles, or as not pregnant before conclusion of the study (December 31, 1994).

Pregnancy rates per cycle for the two insemination methods were compared by \(\chi^2\)-test. Furthermore, cumulative pregnancy rates according to the Kaplan–Meier life-table method were compared by log-rank test. In the life-table analysis, patients alternated in the life-table constructed for insemination by straw and in that for insemination by cervical cap, due to the cross-over design of the study. \(P < 0.05\) was considered to be significant.

Table I. Patient characteristics

<table>
<thead>
<tr>
<th>Indication for artificial insemination by donor</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azoospermia</td>
<td>38</td>
</tr>
<tr>
<td>Severe oligozoospermia(^a)</td>
<td>40</td>
</tr>
<tr>
<td>Miscellaneous(^b)</td>
<td>13</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>31.6 (± 4.2)</td>
</tr>
<tr>
<td>Duration of infertility (years, mean ± SD)</td>
<td>3.5 (± 2.9)</td>
</tr>
<tr>
<td>Nature of infertility</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>67</td>
</tr>
<tr>
<td>Secondary</td>
<td>24</td>
</tr>
</tbody>
</table>

\(^a\)Semen not suitable for conventional in-vitro fertilization (IVF).

\(^b\)Anti-sperm antibodies, chromosome anomalies in the male, repeated total fertilization failure in conventional IVF.

Results

Of the 100 women participating in the study, nine had to be excluded in their first cap cycle, because a narrow cervical canal made placement of the reservoir impossible. The remaining 91 subjects were treated according to the study protocol. Patient characteristics are given in Table I. Four patients with anovulation and two with irregular cycles received ovulation induction, overall in 21 cycles (17 clomiphene citrate, four human menopausal gonadotrophin). In total, 486 treatment cycles were completed with a median of 5.3 cycles per patient. The overall conception rate was 57.1% per patient (52/91) and 10.7% per cycle (52/486). Patients were inseminated by straw in 236 cycles resulting in 14 pregnancies (5.9% per cycle). Insemination by cap was performed in 250 cycles yielding 38 conceptions (15.2% per cycle). The difference in conception rates between the two groups was significantly different (\(\chi^2 = 9.96, P < 0.001\)).

Three life-tables were constructed to facilitate comparison of cycle-specific cumulative conception rates (CCR): one for all treatment cycles, one for cervical cap cycles, and one for straw cycles (Figure 2). The CCR after 12 treatment cycles was significantly higher with insemination by cervical cap as compared with insemination by straw (log-rank test, \(P < 0.005\)).

During the course of the study, cycle monitoring and timing of insemination were changed from BBT to urinary LH testing. To examine the possible confounding effect of cycle monitoring

Figure 1. The cervical cap held in forceps in the position in which it is placed against the cervix. The reservoir shown on top is placed in the cervical canal. The nylon string is left protruding from the cervix to allow easy removal by the patient.
on pregnancy rates, cycles were analysed separately according to technique of insemination and method of monitoring (Table II). In cycles inseminated by cervical cap, the difference in pregnancy rates between LH- and BBT-monitored cycles was statistically significant \((P = 0.04)\). In cycles with intracervical insemination by straw no difference was apparent. Overall, insemination by cap performed better than insemination by straw, regardless of the method of monitoring. There were no differences in age, parity, number of inseminations per cycle and male infertility diagnosis in women who became pregnant with either insemination method and those who failed to conceive (data not shown).

The status of all patients at completion of the study is given in Table III. In the group that switched to a different treatment method, five were given IUI because of poor cervical mucus characteristics, six switched to IUI with ovulation induction after six unsuccessful cycles because of advanced age, four were diagnosed with tubal pathology necessitating reconstructive microsurgery or IVF, and four patients conceived by means of gamete intra-Fallopian transfer performed in conjunction with a diagnostic laparoscopy.

Although patients’ attitudes to either insemination method was not systematically evaluated during this study, most patients preferred the cap method, because it limited the time per insemination spent in the clinic. Removal of the cap was easily accomplished by all subjects.

Table II. Pregnancy rate per cycle according to method and timing of insemination (percentages in parentheses)

<table>
<thead>
<tr>
<th>Cervical cap</th>
<th>Straw</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBT</td>
<td>26/201 (12.9)*t</td>
<td>13/196 (6.6)*</td>
</tr>
<tr>
<td>LH</td>
<td>12/49 (24.5)**t</td>
<td>1/40 (2.5)**</td>
</tr>
<tr>
<td>Total</td>
<td>38/250 (15.2)***</td>
<td>14/236 (5.9)***</td>
</tr>
</tbody>
</table>

BBT = basal body temperature  \( \text{LH} = \) luteinising hormone

*Cap versus straw, \( \chi^2 = 4.45, P = 0.04 \). In cycles with intracervical insemination by straw no difference was apparent. Overall, insemination by cap performed better than insemination by straw, regardless of the method of monitoring. There were no differences in age, parity, number of inseminations per cycle and male infertility diagnosis in women who became pregnant with either insemination method and those who failed to conceive (data not shown).

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Table III. Outcome of treatment during the study period

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pregnant/cycle</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary LH</td>
<td>BBT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barratt et al. (1989)</td>
<td>7/103</td>
<td>5/127</td>
<td>1.78</td>
</tr>
<tr>
<td>Federman et al. (1990)</td>
<td>16/133</td>
<td>7/131</td>
<td>2.42</td>
</tr>
<tr>
<td>Odem et al. (1991)</td>
<td>15/234</td>
<td>27/203</td>
<td>0.45</td>
</tr>
<tr>
<td>Robinson et al. (1992)</td>
<td>9/111</td>
<td>8/123</td>
<td>1.27</td>
</tr>
<tr>
<td>Total</td>
<td>47/581</td>
<td>47/584</td>
<td>0.98</td>
</tr>
</tbody>
</table>

The heterogeneity between studies (Breslow–Day 10.36, \( P < 0.02 \)) is caused entirely by the study of Odem et al., in which two or three inseminations per cycle were performed in the BBT group as opposed to a single insemination in the LH-monitored group. In all other studies, the number of inseminations was identical for both groups.

OR = odds ratio; CI = confidence interval.

Although patients’ attitudes to either insemination method was not systematically evaluated during this study, most patients preferred the cap method, because it limited the time per insemination spent in the clinic. Removal of the cap was easily accomplished by all subjects.

Discussion

The results of this study indicate that pregnancy rates in an AID programme with simple intracervical insemination can be improved by the use of a cervical cap like the Dome de Kremer Belaish. In this study, the number of inseminated spermatozoa was the same for both methods, while in addition patients were inseminated with semen from the same donor throughout the course of the study. A factor that could possibly confound the results obtained in this study was the use of two different monitoring techniques to time inseminations during the course of the study. Indeed, we found a small but significantly different pregnancy rate in cap cycles monitored by urinary LH versus BBT, while such a difference was not apparent in straw cycles (Table II). Since this analysis involved multiple, post-hoc comparisons one should be careful in interpreting these results. In particular, the borderline significance found in the cap cycles should not readily be taken to indicate a real difference. In addition, a meta-analysis of randomized clinical trials examining the benefit of LH-insemination over BBT in AID (Barratt et al., 1989; Federman et al., 1990; Odem et al., 1991; Robinson et al., 1992) showed no difference between the two methods (Table IV).

The higher pregnancy rates observed in cervical cap cycles are therefore likely to be due to the use of the device. It is obvious that the cap prevents backflow of spermatozoa from the cervical canal into the vagina. This may be an important factor in explaining the cap’s improved success rates, since the small insemination volume commonly employed in AID offers virtually no buffering capacity against the acidic vaginal environment. In addition, the intracervical reservoir of the cap prolongs the time during which spermatozoa can enter the cervical mucus, which may be particularly important in view of the poor motility characteristics and reduced survival time.
of cryopreserved spermatozoa as opposed to fresh semen (Critser et al., 1987). Both mechanisms, prevention of backflow and prolonged exposure, may effectively increase the number of spermatozoa available at the site of fertilization, thereby increasing the chance of conception.

In the years preceding this study, donor insemination in our institution was routinely performed by intracervical insemination by straw, yielding a mean success rate of 8.7% per cycle for the first 12 treatment cycles. We were surprised to find a much lower success rate of only 5.9% per cycle for this insemination method during the study period. An explanation for this finding may be found in the cross-over design of the study: subjects are most likely to conceive in cycles where they are exposed to the most successful treatment method, i.e. insemination by cap. Indeed, in fertility trials using pregnancy as the primary endpoint, cross-over studies tend to overestimate the effect of the experimental treatment (Khan et al., 1996).

A recent study addressing this issue with identical methodology (Coulson et al., 1996) has failed to demonstrate any beneficial effect of the use of a cervical cap. The authors propound that the failure of the cervical cap may have been due to the narrow reservoir allowing only a small area of semen–mucus contact. In view of the results of the current study, however, this explanation seems unlikely. An important difference between the two studies is that in the study of Coulson et al. a larger volume of donor semen (0.5 ml) was used. Since the volume of donor semen used for insemination is known to be an important factor in the success rate of intracervical insemination (Le Lannou et al., 1995), this factor may very well have favoured the results of insemination by straw (9.8% per cycle) over the conception rate by cap (7.8% per cycle), resulting in the failure to demonstrate a difference between the two methods. In addition, other unidentified factors may be responsible for the conflicting conclusions reached in the two studies. This observation once more stresses the fact that results obtained in one centre may not necessarily apply in other centres.

In view of all the considerations, we conclude that the use of a cervical cap for insemination of cryopreserved donor semen can be an alternative to intracervical insemination by straw, and may improve pregnancy rates, in particular when a small insemination volume is used.

Acknowledgements
The authors wish to express their gratitude to Mrs M.Kuit-van Harten and Mrs A.G.Günther, fertility nurses, for performing the inseminations.

References


Received on March 24, 1997; accepted on July 3, 1997