Article

Efficacy of IVF using frozen donor semen in cases of previously failed DI cycles compared with tubal infertility: a cohort study

Dr F Guerif

F Guerif1, MH Saussereau1, C Barthelemy1, ML Couet1, O Gervereau1, J Lansac1, D Royere1,2

1CECOS, Biologie de la Reproduction, Département de Gynécologie-Obstétrique et Reproduction Humaine, Centre Hospitalier Universitaire Bretonneau, 37044 Tours, France
2Correspondence: e-mail: royere@med.univ-tours.fr

Abstract

A cohort follow-up study was designed to compare the efficacy of IVF using frozen donor semen (IVF-D) following previously failed DI cycles (unexplained female infertility) and direct IVF-D treatment because of tubal infertility (control group). The cohort comprised 189 couples initiating IVF-D after previously failed DI cycles (n = 126) or directly (n = 63). Couples were followed until completion (success or drop-out for personal or medical reasons). Live births and drop-out were expressed both as rate per cycle and crude cumulative rate. Characteristics of IVF-D cycles were similar between the two groups. Moreover, overall outcome was also similar in terms of crude cumulative live birth rate (54.0 versus 57.1% for failed DI cycles and tubal infertility groups respectively). This is the first report on crude cumulative live birth rate based on a cohort follow-up study in unexplained previously failed DI cycles and tubal infertility. Previously failed DI cycles did not impair the chances of achieving a successful pregnancy using IVF-D in this series. Slight oocyte dysfunction, which might underlie the failure of DI cycles, might be overcome using IVF-D.

Keywords: cohort, crude cumulative live birth rate, donor insemination, frozen donor semen, IVF, unexplained female infertility

Introduction

The introduction, development and widespread use of intracytoplasmic sperm injection (ICSI) have been highly effective in overcoming severe male infertility (Palermo et al., 1992). However, in some cases donor semen still remains an alternative to achieving parenthood (i.e. non-obstructive azoospermia, genetic or viral risk related to male partner). As acquired immunodeficiency syndrome increased in frequency, the use of frozen donor semen was initiated in France by the French CECOS Federation (Centre d’Etude et de Conservation des Œufs et du Sperme) before 1980. Frozen donor semen may be used for donor insemination (DI) (Byrd et al., 1990; Patton et al., 1992; Wainer et al., 1995; Botchan et al., 2001) and for IVF (IVF-D) (Mahadevan et al., 1983; Cohen et al., 1985; Morshedi et al., 1990).

Clinicians treating infertile couples have several aims, the first being to achieve the birth of a healthy child. The health of children born after DI or IVF-D using frozen donor semen is no different from that of the general population and the results available on the psychosocial development of children look reassuring up to the age of 8–10 years (Lansac and Royere, 2001). Clinicians also aim to propose a type of treatment that maximizes the chances of couples achieving parenthood with the least invasive method for the woman. DI is a quite simple, non-invasive method that can be performed initially in consecutive cycles for women in the absence of tubal disease. By contrast, IVF-D is a more invasive method that is either performed initially for women with tubal disorder, or after failed DI cycles. Whatever the method of assisted reproductive technology used, patients need to be clearly informed about their chances of finally having a baby. The cumulative chances of achieving a live birth after a given number of cycles are...
obviously more meaningful than the live birth rate (LBR) per cycle.

A previous study has already reported on relatively high crude cumulative LBR after DI cycles using frozen donor semen in primary infertile couples (Guerif et al., 2002). However some patients despite normal fertility assessment (evidence of ovulation, patent Fallopian tubes, normal appearing uterus, absence of endometriosis) remain unsuccessful after repeated DI cycles (>6) thus suggesting an ‘unexplained female infertility’. In view of the good prognosis of DI cycles in allowing couples to achieve first parenthood, it was speculated whether repeated DI failures might select women with unexplained infertility with poor prognosis as male parameters are controlled by donor semen.

A monocentre cohort-study was designed in the CECOS of Tours to compare the crude cumulative LBR after IVF-D using frozen donor semen in unexplained infertile women after repeated failed DI cycles and women with tubal disease (control cohort). All couples were followed throughout their first parenthood treatment until completion, i.e. the birth of a live baby or ceasing treatment for medical or personal reasons.

Materials and methods

A cohort of 189 couples was referred to the CECOS of Tours between January 1989 and December 1996 and undertook 359 IVF-D cycles in order to achieve first parenthood. Reasons for male infertility in patients who initiated donor treatment comprised non-obstructive azoospermia (66.5%), severe (<1 × 10⁶ spermatozoa/ml) or moderate (1–10 × 10⁶ spermatozoa/ml) oligozoospermia (23.9%), obstructive azoospermia (5.7%), genetic disease (1.7%) and severe (total sperm motility <5%) asthenozoospermia (2.2%). It should be mentioned that from 1989 until 1996, there was a decrease in the percentage of patients with severe or moderate oligozoospermia or asthenozoospermia with the increasing use of ICSI.

Among these couples, 126 women with unexplained infertility (67%) turned to IVF-D cycles after previously failed DI cycles, whereas 63 women with tubal disease (33%) proceeded directly to IVF-D.

During the period of the study, patients in France were not charged for any DI cycles or for four IVF-D cycles. The general procedure for donor recruitment, donor selection and semen cryopreservation has been described elsewhere (Federation CECOS et al., 1989).

Female infertility factors that could affect the outcome of treatment were detected before the initiation of DI cycles. This involved recording of medical history, current physical examination, basal body temperature charts, serum hormone assessment, transvaginal ultrasonographic examination and evaluation of cervical mucus. Tubal patency and uterus normality were investigated by hysterosalpingography or laparoscopy and endometriosis was investigated by laparoscopy. Women from both groups were all primary infertile, aged <38 years and had normal ovulatory cycles (25–35 days), normal basal concentrations of serum FSH, LH, prolactin, normal mid-luteal serum progesterone, no endometriosis and normal uterus. Unexplained infertile women had undertaken at least six failed DI cycles before turning to IVF-D, while others were referred directly for IVF-D because of tubal disease without hydrosalpinx (control group). In addition, all couples attended an interview to discuss the psychological aspects of artificial procreation with donor semen prior to being included on the waiting list.

The ovarian stimulation protocol in IVF-D cycles has been previously described (Guerif et al., 2002). Fertilization was checked 16–18 h post-insemination (day 1). Fertilization rate was defined by the number of embryos as a proportion of the number of oocytes retrieved. Low fertilization rate was defined as a fertilization rate ≤20%. Embryo development was assessed 24 h later (day 2) prior to transfer, according to the developmental stage and to the degree of cytoplasmic fragmentation. Fertilization and embryo culture until day 2 were performed in IVF-50® medium (Scandinavian IVF Science, Göteborg, Sweden). One to three embryos were transferred at day 2, depending on maternal age, quality of the embryos and the rank of the IVF-D cycle. On day 2, only supernumerary grade 1 embryos (4-cell stage with <10% fragmentation) were cryopreserved.

Only live births were taken into account (including results of frozen–thawed embryo transfers). Spontaneous abortions, ectopic pregnancies and pregnancies lost beyond 12 weeks were considered as failed cycles. The end-point of patients’ follow-up was either live birth or withdrawal from the programme. Discontinuing patients were divided into two groups, based on medical or personal reasons. Some patients were denied further treatment for medical reasons involving poor prognosis [poor response to hormonal stimulation, age over 43 years, failure of fertilization or low (<20%) fertilization rate in IVF-D]. Other patients discontinued further treatment for personal reasons (adoption, decision to postpone further treatment, loss to follow-up, divorce or move). Patients were considered as lost to follow-up when they failed to return to follow-up appointments for more than 12 months. Live birth rate and drop-out for medical or personal reasons were recorded for each couple.

Statistics

The results are given as mean values ± SD and were analysed using Statview 4.1 (Abacus Concepts, Berkeley, USA). Analysis of variance (ANOVA) was used, followed by post-hoc comparisons or contingency tables, depending on the parameter being evaluated, with P < 0.05 as the threshold of statistical significance.

Results

The results involved the cohort of 189 primary infertile couples requesting IVF-D cycles after previously failed DI cycles or directly for tubal disease (control group).

Population studied

The mean age of the women was similar in both groups (32.2 ± 2.9 versus 31.5 ± 3.7 years for failed DI cycles and tubal infertility groups, respectively). Similarly, the duration of initial infertility did not differ between groups (6.0 ± 2.8 years).
versus 6.6 ± 2.8 years for failed DI cycles and tubal infertility groups respectively). Women from the failed DI cycle group had undertaken 9.2 ± 2.7 DI cycles (range 6–15) before the initiation of IVF-D cycles.

**Influence of previously failed DI cycles on the outcome of subsequent IVF-D cycles**

An average of 2.0 IVF-D cycles per couple was performed in both groups (range 1–4). Outcome of IVF-D cycles in both groups is shown in Table 1. The mean number of oocytes retrieved per cycle was significantly lower in the failed DI cycle group compared with the tubal infertility group (9.8 ± 4.9 versus 11.0 ± 6.0, \(P < 0.05\) respectively). Similarly, the mean number of embryos obtained per cycle was lower in the failed DI cycle group compared with the tubal infertility group but without statistical significance (4.7 ± 3.4 versus 5.3 ± 4.5 respectively). However, the fertilization and complete failure fertilization rates did not differ between groups. A similar number of embryos were transferred per cycle in both groups.

The live birth rate per cycle and the crude cumulative LBR are shown in Table 2. The crude cumulative LBR for women with tubal infertility was 57.1% and the LBR per cycle was fairly stable throughout the four IVF-D cycles (25.0–31.7% per cycle). The crude cumulative LBR for women with failed DI cycles was 54.0%. However, the LBR per cycle decreased after the first two IVF-D cycles (28.6–33.3 versus 20%).

Couples who failed to conceive using IVF-D cycles decided to stop further treatment mainly for personal reasons (62%) and less often for medical reasons (38%). Personal reasons included adoption (31%), decision to postpone further treatment (28%) and loss to follow-up (22%). The characteristics of couples according to status (success or withdrawal for personal or medical reasons) after the completion of IVF-D cycles are shown in Table 3. Women’s ages did not differ between groups. Women achieving a successful pregnancy had the lowest lengths of infertility and the highest numbers of oocytes retrieved and the highest numbers of embryos obtained per cycle. By contrast, women who were denied further treatment for medical reasons had the longest length of infertility, the lowest number of oocytes and embryos per cycle, with the lowest fertilization rate and the highest rate of complete fertilization failure.

**Table 1. Characteristics of IVF-D cycles for couples with tubal infertility or failed DI cycles.**

<table>
<thead>
<tr>
<th></th>
<th>Tubal infertility</th>
<th>Failed DI cycles</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of couples</td>
<td>63</td>
<td>126</td>
<td>–</td>
</tr>
<tr>
<td>No. of IVF-D cycles</td>
<td>2.0 ± 1.1</td>
<td>1.9 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>No. of oocytes per cycle</td>
<td>11.0 ± 6.0</td>
<td>9.8 ± 4.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>48</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Complete failure of fertilization (%)</td>
<td>7.5</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos per cycle</td>
<td>5.3 ± 4.5</td>
<td>4.7 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>No. of transferred embryos</td>
<td>2.5 ± 0.6</td>
<td>2.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>No. of twins (%)</td>
<td>7 (19)</td>
<td>21 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of triplets (%)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD.

**NS**: not significant.

**Table 2. Live birth rate per cycle and crude cumulative live birth rate in couples with tubal infertility or failed DI cycles.**

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>Tubal infertility</th>
<th>Failed DI cycles</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cycles</td>
<td>No. of live births (%)</td>
<td>% cumulative LBR</td>
</tr>
<tr>
<td>1</td>
<td>63</td>
<td>20 (31.7)</td>
<td>31.7</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>9 (27.3)</td>
<td>46.0</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>5 (25.0)</td>
<td>54.0</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>2 (25.0)</td>
<td>57.0</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>36 (29.0)</td>
<td>57.1</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of IVF-D cycles for couples who succeeded or dropped out for personal or medical reasons.

<table>
<thead>
<tr>
<th></th>
<th>IVF-D success</th>
<th>IVF-D ceased for personal reasons</th>
<th>IVF-D ceased for medical reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of couples</td>
<td>104</td>
<td>53</td>
<td>32</td>
</tr>
<tr>
<td>Women’s age (years)</td>
<td>31.8 ± 3.3</td>
<td>32.6 ± 3.2</td>
<td>31.9 ± 3.0</td>
</tr>
<tr>
<td>Period of infertility</td>
<td>5.6 ± 3.0a</td>
<td>6.0 ± 3.1</td>
<td>6.5 ± 2.5a</td>
</tr>
<tr>
<td>No. of oocytes retrieved per cycle</td>
<td>10.9 ± 5.4a</td>
<td>9.5 ± 4.9b</td>
<td>4.3 ± 2.2ab</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>53a</td>
<td>47b</td>
<td>38ab</td>
</tr>
<tr>
<td>Complete failure of fertilization (%)</td>
<td>3.6a</td>
<td>4.7b</td>
<td>20.5b</td>
</tr>
<tr>
<td>No. of embryos per cycle</td>
<td>5.8 ± 4.2ab</td>
<td>4.2 ± 2.7bc</td>
<td>1.9 ± 1.1bc</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. Values within rows carrying the same superscript are significantly different (P < 0.05).

Discussion

A cohort study was undertaken in the unit to determine the efficacy of IVF-D using frozen donor semen after failed DI cycles (unexplained female infertility). This study was a controlled comparison with the results of standard IVF treatment with donor spermatozoa, using women with tubal infertility as female controls (Hull et al., 1998). A similar outcome has already been reported after IVF with the husband’s spermatozoa in couples with unexplained female infertility following ovulation induction and insemination treatment failure, compared with IVF with the husband’s spermatozoa in couples with tubal infertility (Gurgan et al., 1995).

IVF-D using frozen semen was reported to have a better outcome than overall IVF using fresh husband’s semen; however, fertility status was heterogeneous between couples (Kovacs et al., 1989; Robinson et al., 1993). In this study, all couples investigated were primary infertile. IVF-D using frozen semen has also been reported to be as successful as IVF using the husband’s spermatozoa, but without any distinction between previously failed DI cycles and direct IVF-D (Cohen et al., 1985; Englert et al., 1989). Additionally, similar results have been reported for IVF-D using fresh donor semen following failed DI cycles and IVF with the husband’s semen; however, neither female nor male fertility status was comparable in this study (Vekemans et al., 1987). Since the chances of achieving a live birth after a given number of cycles look more helpful for patients, the present results were expressed as crude cumulative LBR (Wilcox et al., 1993). Thus, in order to avoid overestimating the chances of success, no assumptions were made by life table analysis (Stolwijk et al., 1996; Land et al., 1997).

Turning to IVF-D after previously failed DI cycles was followed by the same cumulative LBR as direct initiation of IVF-D cycles (54.0 versus 57.1% for failed DI cycles and tubal infertility groups respectively). It should be mentioned that the LBR per cycle decreased after the second cycle in women with failed DI cycles, whereas the rate remained stable throughout the four cycles in women with tubal disease.

Failure to conceive can be regarded as a problem of gamete quality and interactions, embryo development and transportation in the preimplantation stages or implantation and subsequent development. IVF is therefore recommended not only for therapeutic reasons but also because of the possibility of learning about the reproductive process in a given couple. The hypothesis that previously failed DI cycles might select more infertile women was not confirmed in this study. Furthermore, no significant difference was observed between groups regarding the main parameters (age, length of infertility, mean number of IVF-D cycles, total number of embryos and mean number of embryos transferred), with the exception of the total number of oocytes retrieved that was lower in women after failed DI cycles than in women with tubal infertility. Slight disturbances in endocrine profile have been reported in women with unexplained infertility (Leach et al., 1997). Moreover, decreased fertilization rates and/or increased total fertilization failure rates have been reported in IVF cycles for unexplained infertility (Navot et al., 1988; Lipitz et al., 1993; Gurgan et al., 1995; Aboulghar et al., 1996). The results do not support such a hypothesis, since the fertilization rate and total fertilization rate were similar in both groups.

The involvement of slight oocyte or sperm dysfunction in unexplained female infertility has already been assessed using standard IVF with tubal infertility and donor spermatozoa as controls (Hull et al., 1998). Interestingly, the results of IVF-D cycles appeared fairly similar in both groups (tubal infertility and unexplained female infertility), bearing in mind the relatively small number of cycles. Based on a greater number of cycles, the results are in agreement with previous studies (Hull et al., 1998).

It might be postulated, as previously proposed, that IVF could combine the benefits of ovarian stimulation, leading to an increased number of oocytes and facilitating gamete interactions. Thus, slight oocyte dysfunction in women after failed DI cycles might be overcome by IVF-D.

The results showed overall that the prognosis of IVF-D after failed DI cycles was comparable to that of IVF-D cycles for tubal disease. Female fertility impairment that might in some way underlie unexplained failure of DI cycles might be overcome using IVF-D.
Acknowledgements

We thank Doreen Raine for correction of the English text.

References


Cohen J, Edwards RG, Fehilly CB et al. 1985 In vitro fertilization using cryopreserved donor semen in cases where both partners are infertile. Fertility and Sterility 43, 570–574.


Gurgan T, Urman B, Yarali H et al. 1995 The results of in vitro fertilization embryo transfer in couples with unexplained infertility failing to conceive with superovulation and intrauterine insemination. Fertility and Sterility 64, 93–97.


Received 27 May 2004; refereed 17 June 2004; accepted 14 July 2004.