Intrauterine insemination with frozen donor sperm. Pregnancy outcome in relation to age and ovarian stimulation regime

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BACKGROUND: The success of intrauterine insemination with donor semen (IUI–DI) is likely to be influenced by a number of variables, including age and ovarian stimulation (OS) regime. METHODS AND RESULTS: A retrospective analysis of 1056 treatment cycles in 261 women (212 single heterosexuals and 49 lesbians) was conducted to assess the influence of these two variables on pregnancy outcome during IUI–DI. The overall pregnancy rate was 10.6%, being 18.5% for women <35 years, 11.9% in women 35–40 years and 5.4% in women >40 years (P < 0.05). The cumulative pregnancy rate (CPR) after eight cycles was 0.86, 0.51 and 0.32 respectively (P < 0.05).

A total of 445 inseminations were performed following spontaneous ovulation, 360 following OS with clomiphene citrate (CC) and 251 with hMG, the pregnancy rate per cycle being 13, 7.2 and 11.2% respectively. There was no statistically significant difference in the pregnancy rate per cycle, CPR or multiple pregnancy rate in the three treatment groups. CONCLUSIONS: These results indicate that the use of OS with either CC or hMG in women without ovulatory dysfunction does not improve the pregnancy rate during IUI–DI. The only factor associated with reduced effectiveness of fertility treatment was age, confirming that IUI is a poor treatment option for women >40 years of age.

Key words: age/donor sperm/IUI/ovulation induction

Introduction

Intrauterine insemination using donor semen (IUI–DI) is a widely accepted and successful treatment for single or lesbian women, or women with azoospermic partners. When compared with intracervical insemination, IUI–DI has a significantly higher success rate per cycle (Wainer et al., 1995; Guzick et al., 1999).

The need to prevent transmission of sexually transmitted diseases has led to the mandatory quarantine of donor semen prior to use and, unfortunately, post-thaw sperm survival, motility and pregnancy rates are affected adversely by both the cryopreservation technique and cryoprotective medium used, with fecundability rates falling from 18.9% to as low as 5% with fresh and frozen–thawed sperm respectively (Ritcher et al., 1984).

Assuming that the women requiring DI are fertile, the success of IUI–DI may be influenced by many variables, such as timing of insemination (Awonuga and Govindbhai, 1999), frequency of insemination, (Khalifa et al., 1995) number of treatment cycles and use of ovarian stimulation (OS) with clomiphene citrate (CC) or gonadotrophins (hMG) (Brzechffa et al., 1998). Although these and other variables have been extensively investigated, there are still limited and controversial data on the effect of women’s age and OS.

Since we considered that the choice of fertility treatment would be related to the age of the woman, we retrospectively reviewed 1056 cycles of IUI–DI in 261 women in order to determine the influence of patient’s age, therapeutic regime and number of treatment cycles on the cycle fecundity of women undergoing IUI–DI treatment with respect to the cumulative pregnancy rate.

Materials and methods

A total of 1056 cycles of IUI–DI were performed on 261 patients (212 single heterosexuals and 49 lesbians) who attended the Bridge Centre between 1993 and 1999. Typically the women were advised to undergo counselling, an extensive clinical interview and a gynaecological examination. Tubal patency was assessed by hysterosalpingography and/or laparoscopy in women with an unremarkable gynaecological history, had risk factors for tubal disease or who had failed to conceive within six treatment cycles.

Patients (n = 10) with ovulatory dysfunction were treated with CC (daily for 5 days, 50–100 mg) or hMG (typically 75–150 units on alternate days). OS was used (n = 106) empirically to increase
the number of oocytes available, with both CC or hMG until 2–3 follicles, diameter 16–20 mm, were seen. The use of OS in the first eight cycles compared with spontaneous ovulation is shown in Table I. In women undergoing OS, transvaginal ultrasonography and serum estradiol (E2) measurements were performed to assess follicular development and reduce the risk of ovarian hyperstimulation syndrome and the insemination was withheld if four or more follicles of 16–20 mm were seen, to reduce the risk of multiple pregnancy.

The optimum time for insemination was decided by the determination of the urinary LH surge by testing urinary LH measurement (Clearplan-Unipath Ltd, Bedford, UK); ultrasound monitoring was followed by 10 000 IU of hCG injection in the stimulated cycles when the leading follicle was >17 mm in diameter. Before 1996, 56 patients received double insemination performed ~36 h after hCG injection or on the same day of the LH surge and then 24 h later. Because of evidence that cycle fecundity was not increased by repeating the insemination, the routine use of a second insemination was abandoned (Khalifa et al., 1995). Other patients received a single insemination only on the day following the LH surge or ~36 h after the hCG injection.

Frozen donor sperm samples were thawed, centrifuged and prepared using discontinuous Percoll gradients (Pharmacia AB, Uppsala, Sweden) until January 1996, after which the samples were prepared with Ixaprep (Medicut-Lerso Parkalle 4Z, DK-2100, Copenhagen, Denmark). Clinical pregnancy was defined as the presence of an embryonic or fetal heart ultrasonically at 6–8 weeks gestation or the identification of trophoblastic tissue histologically as in the case of ectopic pregnancy. Selective fetal reduction was not performed in any patients in this study.

Statistical analysis
Comparison between variables was performed by the χ²-test. The mean values among groups were compared using a standard analysis of variance, P < 0.05 being considered statistically significant. The Bonferroni correction for multiple comparisons was used to adjust the α level for statistical significance (Abt, 1981). Data for life table analysis were performed by previously described methods (Cramer et al., 1979). Log rank test was used to show differences between the curves (Glanz, 1981).

Results
Clinical characteristics and treatment outcome
The women completed 1056 treatment cycles of IUI–DI (mean 4.1, range 1–24). The mean age of the women was 38.3 ± 4.0 years (range 26–47). Of the cycles, 9.7% were cancelled because of anovulation or risk of multiple pregnancy and not included in the analysis. The distribution of the cancelled cycles by age was: 11% in women <35 years old, 9.3% in women 35–40 years and 8.2% in women >40 years, these differences not being statistically significant. The cancellation rate in relation to ovulation was 9.9% in natural cycles, and 10 and 11% after the use of CC and gonadotrophins respectively.

The average cycle fecundity for all attempts was 10.6%. Of the 112 pregnancies (107 singleton, five twins), 78 (70%) led to a delivery, 34 (30%) resulted in miscarriage and two (1.9%) were ectopic pregnancies.

Table I. Spontaneous ovulation and controlled ovarian stimulation with clomiphene citrate (CC) and HMG in relation to the number of cycles undergone by each patient (cycle number). Data from the first eight cycles only are included; n = 951

<table>
<thead>
<tr>
<th>Cycle number</th>
<th>Spontaneous ovulation (%)</th>
<th>CC (%)</th>
<th>HMG (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>137 (55)</td>
<td>71 (28)</td>
<td>42 (17)</td>
<td>253</td>
</tr>
<tr>
<td>2</td>
<td>83 (44)</td>
<td>67 (35)</td>
<td>39 (21)</td>
<td>191</td>
</tr>
<tr>
<td>3</td>
<td>71 (46)</td>
<td>49 (31)</td>
<td>33 (21)</td>
<td>156</td>
</tr>
<tr>
<td>4</td>
<td>39 (37)</td>
<td>45 (41)</td>
<td>23 (21)</td>
<td>107</td>
</tr>
<tr>
<td>5</td>
<td>24 (29)</td>
<td>39 (47)</td>
<td>17 (20)</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>18 (27)</td>
<td>26 (40)</td>
<td>21 (32)</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>16 (29)</td>
<td>23 (42)</td>
<td>16 (29)</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>15 (36)</td>
<td>16 (39)</td>
<td>10 (24)</td>
<td>41</td>
</tr>
</tbody>
</table>

Table II. The number of cycles, pregnancy rate and live birth rate in relation to patient’s age per cycle

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pregnancies/ cycle (%)</th>
<th>Pregnancies/ patient (%)</th>
<th>% Cancellation rate</th>
<th>% Delivery rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>39/211 (18.5)</td>
<td>39/67 (58.2)</td>
<td>11</td>
<td>18.8</td>
</tr>
<tr>
<td>35–40</td>
<td>60/506 (11.9)</td>
<td>60/133 (45.1)</td>
<td>9.3</td>
<td>5.8⁺</td>
</tr>
<tr>
<td>&gt;40</td>
<td>13/339 (5.4)⁺⁺</td>
<td>13/61 (21.3)</td>
<td>8.2</td>
<td>3.0⁺⁺</td>
</tr>
</tbody>
</table>

⁺⁺P < 0.016 significant as for Bonferroni correction for multiple comparison.
Figure 1. Cumulative pregnancy rate (CPR) according to patient’s age (years).

Figure 2. Cumulative pregnancy rate (CPR) according to stimulation regime.

Table III. Treatment outcome in relation to the ovarian stimulation regime per cycle

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pregnancies/ cycle (%)</th>
<th>Pregnancies/ patient (%)</th>
<th>% Cancellation rate</th>
<th>% Delivery rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>58/445 (13)</td>
<td>58/192 (30.2)</td>
<td>9.9</td>
<td>6.8</td>
</tr>
<tr>
<td>CC</td>
<td>26/360 (7.2)</td>
<td>26/134 (19.4)</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>HMG</td>
<td>28/251 (11.2)</td>
<td>28/103 (27.2)</td>
<td>11</td>
<td>5.7</td>
</tr>
</tbody>
</table>

CC = clomiphene citrate.

Follicular development was monitored routinely in every cycle of the women who underwent OS with hMG and at least in the first cycle of the women on CC until a ‘safe’ and effective dose was established. Unifollicular development was seen in 46% of the hMG cycles; two or three mature follicles were seen in 31 and 13% cycles before insemination, 4% were cancelled because of no ovarian response and 6% were cancelled because of the development of more than four mature follicles. Similarly in the women on CC, of the 220 (59%) monitored cycles, unifollicular development was recorded in 55%, two and three mature follicles being seen in 35 and 7% cycles, 2% being cancelled because of no ovarian response and 1% because of the development of more than four mature follicles.

The pregnancy rate in relation to the number of mature follicles was 9.3, 11.2 and 11.5% respectively when one, two or three mature follicles were seen (not significant).

Characteristics of the semen analysis and number of follicles prior to insemination

There was no correlation seen between the number of follicles prior to IUI–DI (1.6 ± 0.8 in the pregnant patients and 1.5 ± 0.8 in non-pregnant women) and the pregnancy rate.

The association between conception and sperm characteristics was examined. The mean number (±SD) of motile sperm inseminated in conception cycles (10.9 ± 7.1×10^6) was not different from the number inseminated for non-conception cycles (11.5 ± 10.2×10^6).

Discussion

The use of OS as empirical therapy to improve the pregnancy rate in women undergoing IUI is common, but as yet of unproven value. Retrospectively analysing these data, we intended to examine the utilization of OS to optimize the treatment in relation to the patient’s age in an IUI programme using frozen–thawed donor sperm.

Recently, the treatment of older single women (heterosexuals or lesbians) with DI has become a major challenge due to an increase in delayed childbearing (Cook and Golombok, 1995; Ferrara et al., 2000).

The effect of fertility treatments in the general population may be better understood from studying single women undergoing DI. Since these women are typically fertile, we are more likely to avoid confounding variables such as the aetiology of infertility. Though pelvic pathology has been reported in the literature ranging from 2 to 72% of women who failed to conceive during DI (Aiman, 1982), we have assumed that women requesting DI do not have the same risk features as a woman who may also have an oligospermic partner (Emperaire et al., 1980).
The results of this large retrospective study demonstrate a decline in both pregnancy rate and CPR with increasing patient age, the vast majority of pregnancies occurring in the first five treatment cycles.

The lowest rates of pregnancy per cycle were seen among the patients >35 (11.9%) and 40 years old (4.5%; P < 0.016; Table II), which is in accord with other reports (respectively 12.4 and 5.6%) (Kang and Wu, 1996). A likely explanation is that both oocyte quality and uterine receptivity decline with age (Meldrum, 1993).

In our study, the CPR analysed according to age after eight cycles was 0.86 in women <35 and 0.51 in women 35–40 years. In older patients, a plateau was evident after six cycles, when the CPR was only 0.32. The younger patients (<35 years old) had a significantly better result than older patients (P < 0.05). Analysis of the CPR in relation to the patient’s stimulation regime did not reveal a statistically significant difference (Figure 2).

The use of OS either with CC or hMG failed to show any statistically significant improvement on fecundity in comparison with spontaneously ovulating women. The use of CC was associated with the lowest fecundity rate when considering age (Table III; Figure 2), these differences not being statistically significant.

The use of OS has not been found to enhance the success rate of IUI–DI (Depypere et al., 1994) and IUI with partner sperm (Huges, 1997), but, in contrast with our results, the use of hMG has been reported to have a favourable effect (Guzick et al., 1993; Lashen et al., 1994). However, only the pregnancy rate per patient was statistically significantly different and not the pregnancy rate per cycle [5 and 18% in natural cycles and 9 and 33% with superovulation in one study (Guzick et al., 1999), and 13 and 32% in natural cycles, 21 and 53% with superovulation in the other (Lashen et al., 1999)]. The pregnancy rate per cycle and the CPR are better measures than the pregnancy rate per patient to determine the likelihood of a patient achieving pregnancy. When counselling a patient who is nearly or >40 years old, it is important to explain the low possibility of pregnancy, as well as the time and the number of treatment cycles needed. A patient aged 35–40 years has a 57% chance of pregnancy, but only after nearly 1 year (Table II).

The fact that different therapeutic regimens failed to effect the pregnancy rate in an IUI–DI programme makes this therapeutic approach for such patients questionable and possibly not beneficial.

Multiple pregnancy is an important aspect of OS that needs to be taken into account, an incidence of 6.5–25% being reported (Chaffkin et al., 1991; Nulsen et al., 1993; Nuojua-Huttunen et al., 1999). In this study, the multiple pregnancy rate was only 4.5% in total (3.6% in spontaneous ovulatory cycles; 3.4 and 7.4% respectively in CC and gonadotrophin cycles; not significant), and 42% of treatment cycles followed spontaneous ovulation. We also did not inseminate patients who produced more than four mature follicles (>14 mm diameter, 19.5% of the cancelled cycles).

Our results show that there is a very low live birth rate (3%) per cycle in women >40 years of age; however, it is higher than the 1.4% reported in infertile couples of the same age from other centres (Frederick et al., 1994).

In contrast to Kang and Wu who described a slight though statistically significant higher pregnancy rate in relation to the number of motile sperm inseminated (Kang and Wu, 1996), in our study there was no evidence of a significant correlation between number of sperm or number of follicles and pregnancy rate. Others have also failed to find differences (Nuojua-Huttunen et al., 1999).

Our results indicate that IUI–DI is a poor treatment option for women >40 years of age and confirm that the woman’s age is a major determinant of the success of any fertility therapy. The success rates of IVF have also been reported to decrease with advancing female age (Hull et al., 1996), indicating that the negative impact of age can only be partly overcome by assisted reproductive technology. Despite this, the cumulative pregnancy rate after three cycles of IVF in women >40 years is 57.8% (Engmann et al., 1999), which makes it reasonable to limit the number of IUI–DI treatment cycles performed in older patients and advise them to consider a more aggressive treatment.

Our data suggest that if pregnancy has not occurred following spontaneous ovulation, the resort to OS either with CC or hMG in women with no proof of ovulation dysfunction does not seems to improve the pregnancy rate in IUI–DI and that the only factor limiting the success of the treatment is age.

Our findings may be biased as this is a retrospective study. Nevertheless, the results are interesting in that they highlight the limitations of OS in improving the effectiveness of IUI–DI. A further prospective randomized study comparing the performance of hMG on IUI versus no treatment showing the results as a life table analysis, may verify or refute our results.

Acknowledgements

The authors are grateful for the expert assistance of Dr Susan Smith and the nursing and embryology staff at The Bridge Centre.

References


Submitted on December 15, 2000; accepted on May 3, 2002