The effect of intercourse on pregnancy rates during assisted human reproduction

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Introduction

The conventional relationship between sexuality and conception is altered by infertility, with many couples reporting diminished sexual activity once they have been diagnosed as infertile (Gervaize, 1993). These difficulties are exacerbated by anxiety and the loss of privacy associated with infertility treatment (Lamont and Anderson, 1993), and may be compounded by the fear that intercourse will ‘dislodge’ the early implanting embryo.

To date, no trial has investigated whether vaginal intercourse around the time of embryo transfer has any influence on the chance of conception during IVF treatment. Hypothetically, intercourse may impair implantation by two principal mechanisms: the introduction of infection and the initiation of uterine contractions. Intercourse has been linked with ascending uterine infection during late pregnancy (Naeye, 1979) and sub-clinical infection of the upper reproductive tract is associated with poor IVF-embryo transfer outcome (Franchin et al., 1998a). During an IVF cycle the uterine cavity is especially vulnerable to intercourse-related infection since the cervical mucous barrier to ascending infection is disrupted by passage of the embryo transfer catheter. Furthermore, uterine myometrial activity is increased during intercourse, especially in the event of female orgasm (Fox et al., 1970). These contractions may interfere with implantation of the early embryo, since high levels of spontaneous uterine activity are associated with poor IVF–embryo transfer outcome (Franchin et al., 1998b).

On the positive side, intercourse may act to assist implantation. Animal studies reveal that exposure to seminal plasma, the fluid component of the ejaculate, is particularly important in animals. Conversely, coitus-induced uterine contractions in the event of female orgasm (Fox et al., 1970) are reported to promote embryo development and implantation. Myometrial activity is increased during intercourse, especially in the event of female orgasm (Fox et al., 1970). These contractions may interfere with implantation of the early embryo, since high levels of spontaneous uterine activity are associated with poor IVF–embryo transfer outcome (Franchin et al., 1998b).

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Materials and methods

Subjects

Couples undergoing thawed embryo transfer at the University of Adelaide’s Reproductive Medicine Units and couples undergoing fresh embryo transfer at the Madrid and Murcia clinics of the Instituto de Fertilidad y Infertilidad between June 1996 and December 1998 were considered for enrolment in the trial. Fresh embryo transfers at the Australian centre and thawed embryo transfers at the Spanish centres were not available for inclusion in the trial because of conflicting research programmes, thereby necessitating the amalgamation of fresh and thawed embryo transfer cycles from the two treatment centres. Women 18–40 years of age in a stable sexual relationship were eligible for enrolment. Exclusion criteria were the use of donor oocytes or spermatozoa, and the presence of hepatitis B, C or human immunodeficiency virus in the male partner. The study was approved by the human experimentation committee of the Instituto Valenciano de Infertilidad (University of Valencia, Spain) and the North Western Adelaide Health Service (University of Adelaide, South Australia).

Power calculations a priori estimated that 1430 embryos would need to be transferred to achieve the statistical power required to detect a 50% improvement in viable pregnancy rates, as seen in the original report (Bellinge et al., 1986) (α = 0.05, β = 0.20, historical pregnancy rate 11% of transferred embryos, 10% cycle cancellation rate).

Clinical IVF protocol

The techniques used to generate oocytes, achieve fertilization and culture embryos have previously been reported for the Australian (Warnes et al., 1997) and Spanish (Pellicer et al., 1996) centres. Briefly, at the Spanish centres a long protocol was used for pituitary desensitization with administration of leuprolide acetate (1 mg/day s.c.; Procrin, Abbott S.A., Madrid, Spain), starting in the luteal phase of the previous cycle. At day 1 and 2 of ovarian stimulation two ampoules of human menopausal gonadotrophin (HMG) were administered (Pergonal; Serono, Madrid, Spain) together with two ampoules of FSH (Fertinorm; Serono). At days 3, 4 and 5 of ovarian stimulation each patient received three ampoules of HMG, with further doses of HMG being tailored on an individual basis according to serum oestradiol concentrations and transvaginal ultrasound scan results. Once an adequate ovarian response had been confirmed (presence of at least two follicles >19 mm in size and a serum oestradiol >2.94 nmol/l), leuprolide and HMG were discontinued and 10 000 IU human chorionic gonadotrophin (HCG, Profasi; Serono) was administered. Transvaginal oocyte retrieval was scheduled 36–38 h after HCG administration, followed by standard IVF or intracytoplasmic sperm injection (ICSI) procedures to achieve oocyte fertilization. All embryos were cultured under standard conditions for 48 h until they had reached the 2–4-cell stage, when they were transferred back to the mother. Intravaginal micronized progesterone (400 mg/day) was routinely used as luteal support in these fresh embryo transfer cycles.

The Australian centres protocol for ovulation induction and fertilization is similar to that used in the Spanish centres and has been previously published (Warnes et al., 1997). Thawed 2-8-cell embryos were transferred to naturally cycling women 3 days following their LH surge. Luteal support was not routinely used in thawed embryo transfer cycles.

Study protocol

Consenting patients attending the Australian centre were randomized either to have intercourse on at least one occasion in a 4 day period encompassing the 2 days before and after embryo transfer, or to abstain during this same period. Patients attending the Spanish centres were randomized to abstain for the entire IVF cycle (as was routine practice at these centres) or to have intercourse on at least two occasions, once in the 12 h before oocyte collection and once 12 h following embryo transfer. The two centres had different protocols for timing of intercourse because it was judged unreasonable to ask couples undergoing fresh embryo transfer to have intercourse shortly following transvaginal oocyte collection. All couples were asked whether they had adhered to their trial allocation.

Study assignment and masking

Randomization was performed using a computer-generated balanced block (n = 4) sequence to generate study allocations, which in turn were sealed in opaque envelopes. The randomization process was stratified according to maternal age (≤35 years, >36 years) and treatment centre. Study allocations for both the Australian and Spanish centres were performed by personnel based in Australia who were not directly involved in patient care.

Participant follow-up

A pregnancy test was performed on day 16 following embryo transfer in all women who had not commenced their menstrual period. Implantation was defined as the presence of a positive urine βHCG or a serum quantitative βHCG ≥20 mIU/ml. All women with a positive pregnancy test had a pelvic ultrasound 4–6 weeks after embryo transfer. All pregnancies at the Australian centre were followed to birth. Outcome data beyond 6–8 weeks gestation were not available for the Spanish participants since the majority of these patients received antenatal care outside the IVF treatment centres.

Analysis

Couples were excluded from the final analysis if they did not reach embryo transfer; however, all couples who reached embryo transfer had their outcome data analysed on an ‘intention to treat’ basis, even if they did not comply with their study allocation. Two-sample t-tests (two-tailed) were used to test for equality of the means of continuous variables. χ² and confidence interval (CI) calculations were used to test the equality of categorical variables. Statistical analysis was performed using SPSS (Version 6.1, SPSS, Chicago, IL, USA) and EpiInfo (Version 6.04b, CDC, Atlanta, GA, USA) software.

Results

Two hundred cycles of thawed embryo transfer and 400 cycles of fresh embryo transfer were enrolled over the course of the trial, with 298 cycles randomized to the ‘abstain’ and 302 to the ‘intercourse’ trial arm (Figure 1). A total of 122 cycles were not included in the analysis since they failed to reach embryo transfer. Of couples randomized to the intercourse trial arm, 22 did not adhere to their trial allocation (illness precluding intercourse, patient withdrawal after randomization); however, the outcome of these couples was still included in the final analysis. No couples randomized to the abstain group reported engaging in intercourse during the study period.

The characteristics of trial participants in the two trial arms were similar, confirming the adequacy of the randomization process. No significant difference in maternal age, past obstetric history or aetiology of infertility was present between the two groups (Table 1). However, a significant difference in the mean number of embryos transferred during each treatment cycle was present between the two trial arms in the Spanish study.
Intercourse during IVF cycles

(intercourse 3.21 ± 1.1 embryos, abstain 3.47 ± 0.89 embryos, P = 0.024). It is conceivable that differences in the number of transferred embryos may reflect differences in embryo quality, since it is common practice to transfer more poor quality embryos in an attempt to bolster the conception rate. Unfortunately the embryologists were blinded to study allocation, making it impossible to comment on the comparative embryo morphology between the two study groups. However, it is unlikely that this difference reflects any significant allocation bias since all other prognostic variables were similar between the two groups.

A total of 1343 embryos was transferred (654 intercourse group, 689 control), with a median of four embryos at the Spanish centre and two embryos per cycle at the Australian centre. This difference reflects the strict legal requirement in South Australia prohibiting transfer of more than three embryos during a treatment cycle.

At the Australian centre 15.7% of treatment cycles resulted in pregnancy, with no significant difference existing between the intercourse and abstain groups [15.4 and 16.1% respectively, odds ratio (OR) 0.95, 95% CI 0.4–2.3] (Table II). At the Spanish centre 26.3% of cycles resulted in pregnancy, but again no significant difference existed between the intercourse and abstain groups [28.5 and 24.2% respectively, OR 1.25, 95% CI 0.72–2.16]. Furthermore, the proportion of biochemical pregnancies that progressed to viable pregnancies did not differ between the intercourse and abstain groups at either the Spanish (88.4% intercourse versus 86.1% abstain, OR 1.23, 95% CI 0.3–5.5) or Australian centres (64.3% intercourse versus 57.1% abstain, OR 1.35, 95% CI 0.23–8.1). When the data from the two treatment centres were pooled (Table III), thereby reducing the chance of a type II statistical error, a significant improvement in the proportion of transferred embryos viable at 6–8 weeks gestation was seen in the intercourse group compared with the abstain group (11.01 versus 7.69 viable embryos per 100 transferred, P = 0.036, OR 1.48, 95% CI 1.01–2.19).

Discussion

The results of this study are the first to provide evidence that intercourse during the peri-transfer period of an IVF cycle is not harmful to early pregnancy outcome. Conversely, women exposed to semen via sexual intercourse exhibited a significant improvement in the proportion of transferred embryos viable at 6–8 weeks gestation was seen in the intercourse group compared with the abstain group (11.01 versus 7.69 viable embryos per 100 transferred, P = 0.036, OR 1.48, 95% CI 1.01–2.19).

Table I. Baseline characteristics of trial participants according to treatment assignment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Australian centre</th>
<th>Spanish centres</th>
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<tbody>
<tr>
<td></td>
<td>Intercourse</td>
<td>Abstain</td>
</tr>
<tr>
<td>Age (years)</td>
<td>33.8 ± 4.4</td>
<td>33.1 ± 4.4</td>
</tr>
<tr>
<td>Median no. of live births (range)</td>
<td>0 (0–5)</td>
<td>0 (0–5)</td>
</tr>
<tr>
<td>Median no. of non-viable pregnancies (range)</td>
<td>0 (0–5)</td>
<td>0 (0–5)</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>5.0 ± 2.5</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td>Aetiology of infertility (% of total)</td>
<td>Male factor</td>
<td>48.4</td>
</tr>
<tr>
<td></td>
<td>Female factor</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>Unexplained</td>
<td>16.5</td>
</tr>
<tr>
<td>Median no. of previous embryo transfer procedures (range)</td>
<td>2 (1–10)</td>
<td>2 (1–9)</td>
</tr>
<tr>
<td>Median no. of embryos transferred during trial cycle (range)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
</tbody>
</table>

Figure 1. Assignment of study subjects.
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Table II. Primary outcome according to treatment assignment

<table>
<thead>
<tr>
<th></th>
<th>Australian centre</th>
<th>Spanish centres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intercourse</td>
<td>Abstain</td>
</tr>
<tr>
<td>Cycles reaching embryo transfer</td>
<td>91</td>
<td>87</td>
</tr>
<tr>
<td>No. embryos transferred</td>
<td>168</td>
<td>171</td>
</tr>
<tr>
<td>Biochemical pregnancies</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Viable singleton</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Viable twins</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Viable triplets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Viable quadruplets</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-viable singleton</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1 viable/1 non-viable</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No. cycles showing evidence of pregnancy (%)</td>
<td>(15.4)</td>
<td>(16.1)</td>
</tr>
<tr>
<td>No. of transfer procedures resulting in a viable embryo(s) (%)</td>
<td>(9.9)</td>
<td>(9.2)</td>
</tr>
<tr>
<td>No. viable embryos per 100 embryos transferred</td>
<td>6.55</td>
<td>4.68</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; NS = not significant.

Table III. Pooled pregnancy outcome data from the Australian and Spanish centres

<table>
<thead>
<tr>
<th></th>
<th>Intercourse</th>
<th>Abstain</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles reaching embryo transfer</td>
<td>242</td>
<td>236</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>654</td>
<td>689</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No. of transfers showing evidence of pregnancy (%)</td>
<td>57</td>
<td>50</td>
<td>NS</td>
<td>1.15</td>
</tr>
<tr>
<td>No. of transfers resulting in a viable embryo (%)</td>
<td>(23.6)</td>
<td>(21.2)</td>
<td>NS</td>
<td>(0.73–1.8)</td>
</tr>
<tr>
<td>No. of viable embryos per 100 embryos transferred (6–8 week ultrasound)</td>
<td>47</td>
<td>39</td>
<td>0.036</td>
<td>1.48</td>
</tr>
<tr>
<td>No. of viable embryos per 100 embryos transferred (6–8 week ultrasound)</td>
<td>11.01</td>
<td>7.69</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

analysis. The 22 non-compliant couples, all of whom abstained, had a pregnancy rate of only 6.35 per 100 transferred embryos, well below that seen in the compliant intercourse group (11.01), yet similar to that seen in the abstain group (7.69).

It could be suggested that natural conception may explain the improvement in pregnancy outcome seen in the intercourse group. This is unlikely to be the case for three reasons. First, the average duration of infertility in our study cohort was 4.7 years. The spontaneous fecundity rate for couples experiencing infertility of >4 years duration is reported to be <1% per menstrual cycle (Collins et al., 1983). This observation, combined with the facts that oocyte retrieval harvests the majority of pre-ovulatory follicles in the fresh embryo transfer cycles and that intercourse occurred in the post-ovulation non-fertile period in the thawed embryo transfer cycles, would ensure that natural conception is unlikely to occur.

The observation that semen exposure had a stronger effect on pregnancy outcome in the Spanish compared to the Australian trial may be explained by several factors. First, couples enrolled in the Spanish trial were asked to have intercourse on two occasions, whereas the Australian group was only required to have intercourse on at least one occasion. The stronger benefit of semen exposure in the Spanish trial may simply reflect a dose-response effect. Second, couples randomized to the abstain arm at the Spanish centre were precluded from having intercourse for the entire treatment cycle, while Australian couples were only asked to abstain for 2 days before and after embryo transfer. If the beneficial effect of semen exposure persists for more than 2 days, couples in the abstain group at the Australian centre may have benefitted from recent intercourse outside the study abstinence period.

Finally, the smaller number of pregnancies in the Australian trial, a reflection of the inferior pregnancy rate inherent in the average duration of infertility in our study cohort was 4.7 years. The spontaneous fecundity rate for couples experiencing thawed embryo transfers, and the lower number of transferred embryos, makes it more difficult for any positive trend in pregnancy outcome to become statistically significant. It is also possible that physiological differences between stimulated (fresh embryo) and unstimulated (thawed embryo) IVF cycles may alter the responsiveness of the female reproductive tract to semen. Alternatively, fresh and thawed embryo metabolism may be different, resulting in altered responsiveness of the embryos to semen-initiated changes in the female reproductive tract.

The mechanism by which semen might benefit early embryo development is presently unknown. In rodents, a lack of exposure to seminal plasma results in a decrease in the rate of preimplantation embryo cleavage (O et al., 1988) and a reduction in the proportion of transferred embryos that successfully implant (Vickery et al., 1969). In humans, seminal plasma pessaries have been successfully used to enhance
implantation rates in women experiencing recurrent miscarriage of unknown origin (Coulam and Stern, 1995). Hence it is possible that semen mediates its positive effect on pregnancy outcome through a combination of preimplantation and early implantation events. Couples undergoing assisted reproduction treatment have a higher rate of early pregnancy loss than fertile couples, with 70% of embryos being lost within 16 days of embryo transfer (Simon et al., 1999). In this study, no significant difference in the rate of clinical miscarriage was observed between the intercourse and abstain groups, thereby indicating that improvements in early embryo survival must be responsible for the increase in viable embryos observed in the intercourse group. Since abstinence is common during IVF treatment cycles, a lack of exposure to semen may play a significant role in the high rate of early embryo attrition observed during IVF treatment.

We have previously postulated that immune-active compounds such as transforming growth factor beta (TGFβ) and prostaglandin E, both present in high concentrations in human semen, may be responsible for the beneficial effect (Robertson et al., 1997). In mice, exposure of the uterine epithelium to seminal TGFβ induces synthesis of pro-inflammatory cytokines including granulocyte-macrophage colony-stimulating factor (Tremellen et al., 1998), which is reported to accelerate preimplantation embryo cleavage and hatching in both mice and humans (Robertson and Seamark, 1992; Robertson et al., 1999; Sjoblom et al., 1999).

There is also evidence to suggest that semen may contribute to the induction of immunological tolerance towards paternal transplantation antigens, thereby favouring the survival of the semi-allogeneic conceptus (Robertson et al., 1997). Adverse immune responses towards trophoblast antigens have been linked with recurrent miscarriage, a late form of implantation failure, while tolerant maternal immune responses are associated with pregnancy success (Hill et al., 1995; Piccinini et al., 1998). Semen contains paternal transplantation antigens and prostaglandin E and TGFβ, with the latter two compounds reported to have immune-deviating activity capable of initiating tolerance towards foreign antigens (Wilbanks and Streilein, 1992; Kelly et al., 1997). There is evidence in rodents to suggest that semen exposure can initiate paternal antigen-specific immune tolerance (Lengerova and Vojtiskova, 1963; Robertson et al., 1997), and in humans observations surrounding the aetiology of pre-eclampsia also support this proposal. The incidence of pre-eclampsia, a disorder believed to be caused by an overly aggressive maternal immune response towards paternal trophoblast antigens ( Dekker and Sibai, 1999), is diminished in women following prolonged exposure to a partner’s semen, with this protection being partner-specific (Martí and Herrmann, 1977; Klonoff et al., 1989; Robillard et al., 1994). Acute exposure to semen around the time of embryo transfer may boost immunological memory in leukocytes reactive against paternal antigens, thereby strengthening immunological tolerance which, at least in animal studies, is known to have limited longevity (Tafuri et al., 1995).

This study is the first to indicate that intercourse during the peri-transfer period of an IVF cycle is beneficial to pregnancy outcome. This is important information to convey to infertile couples since abstinence is commonly practised during infertility treatment and often recommended by the treating physician. Encouraging couples to engage in intercourse during IVF treatment might also have additional psychological advantages in terms of normalizing the ‘conception’ process by allowing couples to participate actively in their reproductive outcome.

References
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