Pregnancy and childhood health and developmental outcomes with the use of posthumous human sperm

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ABSTRACT: Although there is now considerable experience in obtaining sperm from a cadaver, there is little or no published data regarding pregnancy, birth and long-term childhood health and development outcomes when posthumous sperm is used in in vitro fertilisation (IVF). We report the results from treatment of four women undergoing IVF treatment using posthumously acquired human sperm from their deceased partners. In all cases, testicular tissue was obtained in a mortuary setting, and the duration from death to posthumous sperm retrieval ranged from 12 to 48 h. The age of women treated ranged from 31 to 41 years. Fertilization rates ranged from 40 to 100%. Singleton pregnancies were obtained for each of the four women. One pregnancy was complicated by preterm birth at 31 weeks; the other three delivered at term. One baby was growth restricted but morphologically normal; the other children had term birthweights in the normal range. All four children were have shown normal health and developmental outcomes, with the follow-up ranging from 1 to 7 years.

Key words: posthumous / post-mortem / sperm / childhood / health / development IVF

Introduction

Although posthumous sperm retrieval (PSR) was first described in 1980 (Rothman, 1980), it remains an uncommon request for most assisted reproductive treatment (ART) units (Kroon et al., 2012). Across most jurisdictions of the world, uncertainties regarding the legal status of such requests, combined with ethical issues relating to the subsequent use of sperm derived from a cadaver, have made dealing with such requests difficult. To add to these difficulties requests for PSR are invariably made with a short window of opportunity and with enormous pressures on all concerned. Although there is now substantial experience in obtaining cadaver sperm (Jequier and Zhang, 2014), there are few published data providing details of pregnancy outcomes for women and offspring when the post-mortem specimens are used in in vitro fertilisation (IVF) (Shefi et al., 2006).

It is possible to obtain sperm from a cadaver using various techniques, including orchietomy, removal of the epididymis, epididymal aspiration or testicular biopsy, all of which are technically simple. However because of the rarity of requests for PSR, there is no accepted and standard approach, although maximizing the amount of testicular tissue obtained from the cadaver is an important consideration (Kroon et al., 2012; Jequier and Zhang, 2014). The probability that viable sperm can be obtained through PSR is closely related to the interval between the man’s death and the retrieval procedure with previous reports of viable cadaver sperm up to 36 h post-mortem (Land and Ross, 2002; Tash et al., 2003; Shefi et al., 2006). Storage conditions for the cadaver, most notably temperature, appear to affect the probability of obtaining viable sperm at PSR (Land and Ross, 2002).

A study of PSR from 14 men, with a mean interval from death to retrieval of just over 20 h, reported motile sperm in 12 cases (Shefi et al., 2006). In the case with the longest post-mortem duration (36 h), epididymal sperm with 5% motility were obtained. In two of the cases, both with a post-mortem interval of 30 h, the retrieved sperm was used for successful conception and each of the two partners ultimately delivered a healthy child. However, to date there are no published data regarding pregnancy and childhood health and development outcomes for the children conceived with cadaver sperm. Sperm obtained so long after death have an obvious risk of DNA damage and since the safety of the child is of paramount importance, data regarding pregnancy and birth outcomes are vital. In this study, we report embryological data, pregnancy outcomes and long-term child health and developmental outcomes in four cases where sperm were retrieved and cryopreserved post-mortem then subsequently used in ART procedures.
Case series

Since the Australian Capital Territory is the only jurisdiction in Australia where the use of cadaver sperm is legal, careful records are maintained of cases managed through this tertiary reproductive medicine unit. Case review was undertaken of the four PSR cases managed, and the follow-up telephone contact was made with each of the families involved. Table I summarizes the important information for each case. Each individual case received extensive ethical consideration and each woman has provided informed consent for the publication of their case report.

Case 1

The patient’s husband was involved in a motor vehicle accident. After 48 h, testicular tissue was obtained at the mortuary by open biopsy. The biopsy sample was mechanically disrupted to release sperm, which were then placed in cryoprotectant (Quinn’s Advantage Sperm Freezing medium with 4-(2-hydroxyethyl)-1-piperazinethanesulfonic acid, SAGE In-Vitro Fertilization, Inc., CT, USA) contained in 0.3 ml plastic straws, then slow frozen using a programmed freezer until reach – 80°C, before being plunging into liquid nitrogen. Prior to the attempt at conception, the woman underwent counselling, extensive investigation and no medical or psychiatric contraindication to pregnancy was identified. Approximately 21 months following the husband’s death, the widow underwent an IVF cycle. This was an antagonist cycle using follitropin alpha (Gonal-F®, Merck Serono, Australia) and cetrotrelax acetate (Cetrotide®, Merck Serono, Australia). Ovulation was induced with chorionic gonadotrophin alfa (Ovidrel®, Merck Serono, Australia), and 10 mature oocytes were obtained. Three straws of sperm were thawed, and the pooled sample was treated with pentoxifylline and enough non-progressive motile sperm were identified to allow intracytoplasmic sperm injection (ICSI) of all 10 oocytes. Five of the inseminated oocytes were fertilized, and one blastocyst-stage embryo was transferred on Day 5 while three embryos were cryopreserved. Vaginal progesterone (Crinone® Merck Serono, Australia) was used for luteal support, and a viable pregnancy was diagnosed on transvaginal ultrasound at 7 weeks. The pregnancy progressed uneventfully, and the patient delivered a female baby weighing 3.1 kg in excellent condition at 38 weeks of gestation (50th centile). Thorough examination by a specialist paediatrician revealed no abnormality, and the mother and baby had an uncomplicated post-natal period. Health and development to age 1 year have been unremarkable.

Case 2

A male aged 39 years died in a workplace accident and testicular tissue was obtained from the cadaver by open biopsy at 23 h post-mortem, with three straws frozen using the CVS Cryosystem. The female partner, aged 41 years, underwent an antagonist protocol, with follitropin beta (Puregon®, Merck Sharp and Dohme, Australia) and ganiirelix acetate (Orgalutran®, Merck Sharp and Dohme, Australia). Ovulation was induced with chorionic gonadotrophin alfa (Ovidrel®, Merck Serono, Australia). Eleven oocytes were collected, and eight were suitable for injection. One straw of sperm was thawed and washed in sperm media and treated with pentoxifylline. Enough motile sperm were found to allow microinjection and all eight oocytes fertilized normally. Two blastocyst-stage embryos were transferred. There were no embryos suitable for cryopreservation. The pregnancy was complicated by cervical shortening managed with hospitalization and rest, but birth was preterm at 31 weeks of gestation. The baby, a male infant weighing 1.63 kg (50th centile), was delivered vaginally in good condition, but remained in hospital for 7 weeks until discharge at 39 corrected weeks of gestation. The post-natal course was normal, and subsequent health and development to 4 years, with close paediatric surveillance, has not revealed any concerns.

Case 3

A male aged 39 years died in a workplace accident and testicular tissue was obtained from the cadaver by open biopsy at 23 h post-mortem, with three straws frozen using the CVS Cryosystem. The female partner, aged 41 years, underwent an antagonist protocol, with follitropin beta (Puregon®, Merck Sharp and Dohme, Australia) and ganiirelix acetate (Orgalutran®, Merck Sharp and Dohme, Australia). Ovulation was induced with chorionic gonadotrophin alfa (Ovidrel®, Merck Serono, Australia). Eleven oocytes were collected, and eight were suitable for injection. One straw of sperm was thawed and washed in sperm media and treated with pentoxifylline. Enough motile sperm were found to allow microinjection and all eight oocytes fertilized normally. Two blastocyst-stage embryos were transferred. There were no embryos suitable for cryopreservation. The pregnancy was complicated by cervical shortening managed with hospitalization and rest, but birth was preterm at 31 weeks of gestation. The baby, a male infant weighing 1.63 kg (50th centile), was delivered vaginally in good condition, but remained in hospital for 7 weeks until discharge at 39 corrected weeks of gestation. The post-natal course was normal, and subsequent health and development to 4 years, with close paediatric surveillance, has not revealed any concerns.

Case 4

The patient’s partner, aged 29 years, was killed in a motor vehicle accident and testicular tissue was obtained by open biopsy 24 h post-mortem, then stored in straws using the CVS Cryosystem. The female patient was 38 years old at the time of treatment. At first, there were two unsuccessful IVF cycles with low oocyte numbers and poor quality

<table>
<thead>
<tr>
<th>Case</th>
<th>Duration post-mortem (h)</th>
<th>Maternal age (years)</th>
<th>Number of cycles</th>
<th>Gestation at birth (weeks)</th>
<th>Birthweight (centile)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>31</td>
<td>1</td>
<td>38</td>
<td>3.1 kg (50th)</td>
<td>12 months</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>38</td>
<td>1</td>
<td>40</td>
<td>2.85 kg (&lt;10th)</td>
<td>5 years</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>41</td>
<td>1</td>
<td>31</td>
<td>1.63 kg (50th)</td>
<td>4 years</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>38</td>
<td>3</td>
<td>39</td>
<td>3.1 kg (25th)</td>
<td>7 years</td>
</tr>
</tbody>
</table>
Discussion

In each of the four cases, viable sperm were obtained from thawed specimens of testicular tissue retrieved from cadavers, the longest duration being 48 h from the declaration of death to the retrieval procedure in the mortuary. This period of 48 h is the longest published interval for posthumously collected sperm resulting in a healthy live birth. This is significant as prior case series had suggested posthumous collection was only possible up to 36 h (Shefi et al., 2006). In all four cases, fertilization rates ranged from 40 to 100%, and healthy babies were delivered for each of the women. In three of four cases, the birthweights were normal; in the one case where there was evidence of a low birthweight, the same finding had been noted in the older, naturally conceived sibling. All children have had close paediatric follow-up and have no health or developmental problems, with the oldest now aged 7 years.

In the three decades since the first description of PSR, there has been increasing public awareness and media interest in the topic. However, the rarity of the procedure has often precluded development of standard protocols and procedures for dealing with PSR requests (Kerr et al., 1997; Check et al., 1999; Bahadur, 2002; Check et al., 2002; Land and Ross, 2002; Batzer et al., 2003; Hill, 2003; Tash et al., 2003; Shefi et al., 2006). The typical recommendation is that PSR should be performed within 24 h of death (Jequier and Zhang, 2014) with a previously reported upper limit of 36 h (Shefi et al., 2006), although our series has now shown that viable sperm can be obtained from a cadaver 48 h after certification of death. Because different techniques have been used for PSR, it has not been possible, to date, to provide good evidence as to which technique is most appropriate.

Although the various techniques employed to retrieve post-mortem sperm are technically simple, the legal and ethical issues that must be addressed are complicated. The situation where a man has clearly left antemortem instructions for PSR is extremely rare, but this would make the ethical consideration less ambiguous. Unfortunately, in almost all cases there is no explicit written consent for PSR and the request comes from the partner or other family member. In this situation, there is no clarity as to whether the deceased man would wish for PSR, with its implication that the conceived child would have no contact with the father. In some cases, there might be evidence that a couple was planning pregnancy such as fertility investigations or treatment. Even in such a case, there is unlikely to be any evidence that the deceased would wish for PSR. Recently, it has been argued that posthumous conception should be allowed provided that a man has not previously expressed a wish not to be a participant in the event of his death. This approach is required since very few men actually record their wishes to be involved in posthumous conception in the unlikely event of their death, and most deaths in the reproductive age group are unexpected. For a full discussion of these issues, the reader is referred to Tremellen and Savulescu (2015). An important but commonly unreported consideration is that subsequent legal proceedings can occupy 2 or more years, and during this delay, there is considerable potential for the female partner’s fertility status to worsen. This needs to be considered by jurisdictions involved in legal decision-making.

Ethical guidelines from the Australian National Health and Medical Research Council (NHMRC, 2007) are in line with those of the European Society for Human Reproduction and Embryology (Pennings et al., 2006) and American Society for Reproductive Medicine (ASRM, 2004) in assigning a pivotal role for explicit antemortem consent. Legislation regarding ART in Australian jurisdictions varies, but does not specifically deal with issues pertaining to PSR (Kroon et al., 2012). For example in some states, PSR can be undertaken either by order of the coroner, or with the antemortem explicitly documented consent of the deceased. In other states, equivalent legislation has been held by the Courts not to go so far as to allow the removal of sperm. Even if PSR is performed by Court order, use of the cryopreserved sperm in ART may still be illegal. For example, in some states sperm may only be used posthumously if it was retrieved prior to death.

This study and others have demonstrated that viable sperm can be obtained after PSR and cryopreservation, but with a new upper limit of 48 h after death. In all four of our cases, posthumously acquired sperm have yielded healthy babies who have grown into developmentally normal children. Given the urgency with which most requests for PSR are received, it is time to develop widely accepted guidelines to allow informed counselling of widowed partners and families and to guide ART unit staff in their use.

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Authors’ roles

S.J.R., S.C., J.M. and K.T. are all IVF physicians who personally managed these cases, and the follow-up of mothers and babies was conducted by S.J.R., E.C. and G.M. are embryologists who managed the IVF laboratory procedures. All authors contributed to writing the paper.

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Conflict of interest

None declared.

References


