The acceptability of posthumous human ovarian tissue donation in Utah

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BACKGROUND: Infertility due to accelerated loss of ovarian follicles/oocytes may occur through numerous mechanisms. As a result, posthumous human oocyte donation, banking and maturation protocols for research and fertility restoration are current interests in reproductive medicine. METHODS: A computer-generated sample of Utah residents (n = 704) were surveyed regarding demographics, willingness to donate organs, IVF acceptability and posthumous follicle/oocyte donation for: research, fertilization with monitoring to the preembryo stage (eight cells), and fertilization and subsequent transfer of embryos derived from themselves, their partner or non-spousal relative for whom they act as guardian. RESULTS: Ovarian tissue donation for follicle/oocyte retrieval, maturation and scientific investigation without fertilization was acceptable (≥70%) to a majority of the Utah population. However, fertilization of oocytes or fertilization and transfer of resulting preembryos derived from such donations to cause a pregnancy was less acceptable (58.3% and 57.4%, respectively) in the population responding for their own or partner’s oocytes, and more so when the donation was guardian-directed (54.8% and 52.1%, respectively). Similar declines in the level of acceptance were noted when those who had an express interest in such donations (ovarian failure or surgical castration) were surveyed (n = 50). CONCLUSIONS: This study substantiates the ethical recommendation that explicit prior written consent of the donor be obtained when ovarian tissue donations are procured for fertilization, or transfer of a preembryo to cause a pregnancy. In light of the rapid technological advancements in ovarian follicle/oocyte cryopreservation and maturation, the time may have come to provide potential organ donors the opportunity to specify their desires regarding ovarian tissues when registering for organ donation.

Key words: IVF/oocyte donation/organ donation/posthumous ovarian donation/premature ovarian failure

Introduction
The fundamental unit of the mammalian ovary is the ovarian follicle containing the oocyte. Ovarian follicles begin their development as primordial structures consisting of an oocyte arrested in the dictyate stage of prophase 1, surrounded by a few flattened granulosa follicular cells. At birth, the human species has approximately 2–3 million primordial follicles. By puberty the number of follicles remaining has decreased to 200 000–400 000. In response to factors and events not yet fully characterized, primordial follicles are activated and recruited to develop into primary, preantral, antral and finally mature follicles capable of releasing a fertilizable oocyte. Once the antral stage is achieved, additional further growth is critically dependent on responsiveness to gonadotropin stimulation and other factors. Those follicles unable to respond beyond the antral stage undergo atresia, the ultimate fate of the majority of follicles and their oocytes (Gougeon et al., 1992). Understanding the factors and processes that initiate the activation of primordial follicles (storage form) and cause the majority of preantral follicles to undergo atresia are of particular research interest. Numerous investigators are clarifying the physiology of follicular development and studying the potential to modify and enhance reproductive capacity through that improved understanding (Vitt et al., 2000; Gosden et al., 2002; Johnson et al., 2004).

In the clinical arena, the accelerated loss of primordial follicles/oocytes resulting in infertility may occur through surgical castration for gynaecological conditions, autoimmune mechanisms, genetic programming, chemotherapy and/or radiation. As a result of these conditions, human oocyte donation, banking and in-vitro maturation protocols (both heterologous and autologous) for the restoration of fertility are current interests in reproductive medicine. While animal and human studies performed to date on the cryopreservation and in-vitro maturation of ovarian follicles/oocytes have provided a groundwork, future advances will be required for the clinical use of human follicles.
A unique source of follicles/oocytes for research and innovative fertility restoration therapy is the posthumous donation of ovarian tissues at the time of organ donation. While posthumous ovarian donation may be beneficial both clinically and for research purposes, ethical and societal concerns regarding the ethics of posthumous donation must be addressed prior to widespread implementation. This survey of a representative sample of the Utah population and individuals with an express interest in follicle/oocyte donation was conducted to assess the acceptability of posthumous ovarian donation.

Materials and methods

During 1998–1999, using an institutional review board (IRB)-approved questionnaire and protocol based on a computer-generated population sample that accounted for the demographics of all counties in Utah, a combination of direct encounters (n = 101) in a pilot study and random digit dialing [n = 603; standard error of the mean (SEM) 4.0%] was used to survey residents throughout the state of Utah (group 1). The SEM for the total sample population (n = 704) was ±2.7%. Utah residents (n = 704) were surveyed in a scripted interview regarding demographics (age, gender, religion, educational level, occupation, number of children), willingness to donate organs, the acceptability of IVF, and posthumous follicle/oocyte donation for: research, fertilization with monitoring to the preembryo stage (eight cells), and fertilization and subsequent transfer of developed embryos derived from themselves, their partner or a non-spousal relative for whom they are the legal guardian (Table I). For this survey of lay persons, the term ‘legal guardian’ was used to define not only a court appointed individual to make personal decisions for a ward of the court implementing a best interests standard, but also a surrogate decision maker who is entrusted to make personal decisions based on...
a substituted judgment standard. For the three county pilot study \((n = 101)\), individuals were randomly surveyed by trained non-medical interviewers in a University of Utah Health Sciences Clinic (71%) and mall intercept (29%) sample design that was conducted with the following demographic quotas: 51 in Salt Lake County (29 through the Obstetrics and Gynecology Clinic, 12 at the Surgery/Urology Clinic, and 10 at the Crossroads/ZCMI Mall); 31 in Utah County (21 at the Reproductive Endocrinology/ Gynecology Clinic and 10 at the University Mall); and 19 in Weber County (10 at the Reproductive Endocrinology/Gynecology Clinic and nine at the Ogden Mall). The computer-assisted telephone interview random digit dialing protocol to survey residents of the state \((n = 603)\) utilized standard state demographic quotas, four replicates for the sample, five callbacks, 15% random verification and random selection of adult interviewer (Venture Data, LLC). There were no differences in the pilot study subpopulation \((n = 101)\) compared with those surveyed by random digit dialing \((n = 603)\), thus these were combined as group 1.

To determine whether a group of individuals with a strong potential interest in posthumous follicle/oocyte donation (women and partners requiring oocyte donation for pregnancy) felt similarly to the survey population (group 1), patients with ovarian failure (Turner’s Syndrome, autoimmune, chemotherapy- and radiation-induced, and genetic causes) or ovarian removal for various causes were also polled using the same IRB-approved survey protocol \((n = 50)\) (group 2) in 2000–2001. Interviewees were randomly selected from a list of potential recipients of oocytes receiving treatment at the Utah Center for Reproductive Medicine \((n = 31)\) as well as individuals who responded to the survey posted on the Turner’s Syndrome Society website \((n = 19)\). Standard descriptive statistics and confidence intervals were tabulated. In addition, chi square analysis was performed to determine differences between or among groups. Significant differences \(P < 0.05\) were reported.

**Results**

The results of the survey are detailed in Figure 1. In group 1 (statewide), 397 women and 307 men were surveyed between 18–84 years of age (mean age \( \pm \) SEM, 42.3 \( \pm \) 0.59 years). In Utah, 84.8% \((597/704)\) claimed a Christian religious affiliation: 65.3% \((460/704)\) in the Church of Jesus Christ of Latter-day Saints and 19.5% \((137/704)\) in other Christian denominations. A majority \(70.3\% \(495/704)\) had attended college or beyond. Of the respondents, 69% \((486/704)\) planned to donate organs at death and 70.9% \((499/704)\) planned to donate organs at death and 70.9% \((499/704)\) would encourage others to donate organs at death. Females planned to donate more frequently than men \(78.2\% \(290/371)\) versus 69.0% \((196/284)\); \(P = 0.008\). Females <45 years old were more likely to donate organs than those >45 years old \(84.1\% \(105/232)\) versus 69.1% \((94/136)\); \(P = 0.0008\). IVF was considered acceptable by 89.7% \((615/686)\); 95% confidence interval \((CI)\) 87.4–91.9%. Knowing an infertile couple inc reased the acceptance of IVF \((P = 0.03)\).

The scientific study of oocytes without fertilization was acceptable for 77.1% \((299/388)\); 95% CI 72.9–81.3% of women, and 70.9% \((210/296)\); 95% CI 65.7–76.1% of men. A decreasing level of acceptance was noted when fertilization and potential pregnancies from individually donated or guardian-directed donations were proposed. As a legal guardian (surrogate decision maker), 70.1% \((482/688)\); 95% CI 66.6–73.5% were comfortable with donating oocytes for scientific study without fertilization. When asked regarding the acceptability of donating their own or partner’s oocytes for fertilization and allowing progression to the eight-cell stage without transfer, 58.3% \((398/683)\); 95% CI 54.6–62.0% were comfortable. As a legal guardian only 54.8% \((375/684)\); 95% CI 51.1–58.6% would allow such a donation. Finally, 57.4% \((392/683)\); 95% CI 53.7–61.1%) were comfortable donating their own or partner’s oocytes for fertilization and transfer of the resulting embryos to a couple desiring pregnancy, with 52.1% \((353/678)\); 95% CI 48.3–55.8%) willing to allow such donation as a legal guardian. Males acting as legal guardians were more likely to allow donation to achieve pregnancy than female guardians \(58.1\% \text{ versus } 47.3\%, P = 0.006\). Muslims were opposed to posthumous donation \((n = 2)\). The results of the survey are summarized in Figure 1.

The group 2 survey participants \((40\text{ women, 10 men})\) who had, or their partners had, premature ovarian failure (POF), demonstrated a high level of acceptance \(84\% \text{; 95\% CI 70.9–92.8\%}\) for the study of oocytes without fertilization. This group had an age range of 18–74 years \((\text{mean } \pm \text{ SEM}, 44.9 \pm 1.53)\). In this biased population, 90% had attended college or beyond. Religious affiliations were: 33% in The Church of Jesus Christ of Latter-day Saints and 63% in other Christian denominations \(\text{Catholic 22\%, Greek Orthodox 6.6\%, Episcopalian 6.6\%, Lutheran 6.6\%, other 21\%}\). Fertilization with study to an eight-cell stage as well as preembryo transfer to cause a pregnancy were accepted at a higher level than found in the random \((n = 50)\) population \(80\% \text{ (95\% CI 66.3–90\%)}\) versus 58.3% \((95\% CI 51.1–62.0\%); P = 0.0025; and 76% \((95\% CI 61.8–86.9%)\) versus 57.4% \((95\% CI 53.7–61.1\%), P = 0.01\), respectively. Additionally, fertilization with study of the preembryo to an eight-cell stage after guardian-directed donation was more acceptable in group 2 \([74\% \text{ (95\% CI 59.7–85.4\%)})\] than in group 1 \([54.8\% \text{ (95\% CI 51.1–58.6\%)})\] \(P = 0.008\). However, as with the state survey \((n = 101)\), decreasing levels of acceptability indicative of reservations were evident when fertilization and potential pregnancies from donation and guardian-directed donations were queried (Figure 1).

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**Figure 1.** Acceptance of IVF and posthumous oocyte donation for various purposes. White bars, survey group 1; spotted bars, survey group as legal guardian; black bars, POF group 2; grey bars, POF group 2, as legal guardian. The bar graph headings: ‘IVF’, ‘Oocyte Study’, ‘Fertilize-Prembryo Study’ and ‘Donate for Pregnancy’ refer to survey questions 9, 10–11, 12–13 and 14–15, respectively (see Table I). Error bars represent 95% CIs. Survey group, \(n = 704\); POF group, \(n = 50\).
Discussion

In addition to the research potential of donated human ovarian tissues, actual clinical utility for assisted reproduction may be close to being possible. Despite technical difficulties, notable progress in the cryopreservation, maturation, fertilization and development of embryos from ovarian tissue samples or isolated oocytes is evident. Immature oocytes, from mice and sheep, have been cryopreserved with subsequent in-vitro maturation, fertilization and embryo transfer resulting in live births (Parrott, 1960; Gosden et al., 1994). Cryopreserved marmoset ovarian tissue, xenografted into immunodeficient mice, developed apparently normal antral follicles (Candy et al., 1995). Extended culture of primordial mouse follicles to complete oocyte maturity, with fertilization and subsequent embryonic development and birth, has been recorded (Eppig and O’Brien, 1996). Preliminary studies are underway to culture human primordial oocytes to maturity (Abir et al., 1999).

Human ovarian tissues have been removed, autotransplanted with documented hormonal functional activity and oocyte retrieval (Oktay et al., 2001). Human ovarian tissues have been cryopreserved with successful orthotopic and heterotopic transplantation (Oktay and Karlikaya, 2000; Oktay et al., 2004). Human ovarian tissues and fetal ovarian tissues have been successfully xenografted into immunodeficient mice for later oocyte maturation (Weissman et al., 1999; Abir et al., 2003). Cryopreservation of mature human oocytes, followed by thawing and IVF with embryo transfer and subsequent healthy deliveries was initially reported in the late 1980s (van Uem et al., 1987; Chen, 1988). Since that time, many births have been reported (Porcu et al., 1997; Tucker et al., 1998; Young et al., 1998; Kuleshova et al., 1999; Yoon et al., 2003). Conventionally cryopreserved and vitrified human oocytes have been thawed, fertilized and transferred, resulting in pregnancies (van Uem et al., 1987; Chen, 1988; Porcu et al., 1997; Tucker et al., 1998; Young et al., 1998; Kuleshova et al., 1999; Yoon et al., 2003).

Cryopreservation of mature oocytes has been performed in young women at risk of becoming sterile from gonadotoxic treatments (Poir et al., 2002). Immature (germinal vesicle) oocytes have been matured in vitro, fertilized and transferred resulting in a birth (Young et al., 1998). To date, no successful human pregnancy has been reported with long-term in-vitro maturation of primordial oocytes, owing to multiple technical and structural hurdles (media and support matrices, etc.). However, the technical accomplishments with in-vitro maturation document the capacity to utilize ovarian tissues in a wide range of research and therapeutic endeavors. While posthumous organ donation for therapeutic benefit is now routinely accepted, the possibility of posthumous ovarian tissue donation for therapy and/or research remains hypothetical and non-codified. This study addresses the acceptance and concerns, in defined populations, regarding posthumous ovarian tissue donation.

A previous survey performed in the UK noted widespread acceptance of ovarian tissue donation for research and therapy (688% of their study population) (Kazem et al., 1995). However, in contrast to the present study, only 28% of participants in the UK study found posthumous donations to be acceptable. The difference between the UK and Utah studies may be explained by a greater proportion of ethnic or religious groups in the UK population that view posthumous donation negatively. Alternatively, the strong inclinations of the Utah population towards building families, and their demonstrated willingness to participate in posthumous organ donation and support research endeavors, may also explain the greater level of acceptance of posthumous donation. The Utah results may not be generalizable to other populations; however, recent studies suggest similar rates of acceptability for oocyte donation to help another couple conceive a child. In a German study, 43.2–68.6% of various study populations were willing to donate oocytes for the purpose of conception (Schroder et al., 2004). Similarly, reproductive tissue donation for research appears to be well accepted. For example, in Sweden, 92% of couples with supernumerary embryos from IVF chose donation for stem cell research rather disposal in a recent survey (Bjuresten and Hovatta, 2003).

The lay public’s general acceptance of posthumous ovarian donation for research in Utah, accompanied by significant reservations when the donation is intended for the creation of a pregnancy, supports the published ethical recommendations and practice regarding the donation of organs to prolong life compared with donations intended to create life. In the context of organ donation to prolong life, surrogates are asked to act in accordance with the potential donor’s wishes and value system. However, a higher level of authorization (prior written consent) has been recommended in situations intended to create life. The University of Washington addressed posthumous reproduction in the context of a request to harvest gametes after death (Assisted Reproductive Technology Committee and University of Washington, 1997; Soules, 1999). Their consensus opinion stated that the posthumous donation of gametes for the creation of new life was different from tissue donations given with the intention of prolonging life (i.e. organ donation) or for research. For that reason, they advised explicit prior written consent by potential donors. The Ethics Committee of the American Society for Reproductive Medicine also suggests explicit prior consent for potential posthumous reproduction: ‘A spouse’s request that sperm or ova be obtained terminally or soon after death without the prior consent or known wishes of the deceased spouse need not be honored’ (Ethics Committee and ASRM, 2004).

Surrogate decision makers (guardian-directed) are expected to act according to the wishes of the patient, to the extent they are known or to use the patient’s value system in their decision (Barber v Superior Court, 1983; Harmon, 1990). Unfortunately, surrogates are routinely inaccurate in understanding and executing a patient’s personal preferences (Emanuel and Emanuel, 1992; Sulmasy et al., 1994; 1998; Coppolino and Ackerson, 2001). Further complicating surrogate decision maker’s responsibilities, one legal analysis states that surrogates ‘have the right to take into account other factors, such as the demands of morality and the best interests of the family as a whole’ (Morley, 2002). Some have suggested that surrogates potentially could be authorized to make tissue donation decisions to prolong life if they: (i) can substantially enunciate the patient’s wishes; (ii) derive no benefit from the donation beyond
the altruistic action; (iii) have documentation that the donation will not alter the clinical course; (iv) gain the ethical approval of all participants in the donation procedure; and (v) have had the proposed donation prospectively evaluated by an ethics committee (UCLA Medical Center Ethics Committee and URT Program, 2004). At the present time, a general lack of awareness of the feasibility and utility of posthumous ovarian tissue donation make a clear understanding of the patient’s wishes, approval of participants in the donation process and prospective ethics committee considerations noted above highly problematic for both research and/or therapeutic uses of ovarian tissue.

In summary, this survey of the Utah population (group 1) revealed that both IVF and the posthumous donation of ovarian tissue for scientific investigation was acceptable in a majority of respondents (Figure 1). Donation of follicles/oocytes for scientific investigation, without fertilization, was acceptable in 74.4% of those asked on behalf of themselves or their partner, and in 70.1% of those who would be acting as a surrogate decision maker. When participants were queried regarding fertilization and growth to an eight-cell preembryo, without a resulting transfer of the preembryo, the percentages fell to 58.3% and 54.8% for their own or their partner’s versus guardian-directed donation, respectively. Finally, when fertilization and transfer to a couple desiring a child was proposed, the acceptance levels fell to 57.4% and 52.1% for these groups, respectively. A similar pattern of increasing concern and decreasing acceptance regarding fertilization and potential pregnancies from donation, as well as guardian-directed donations, was noted in a separate survey of those who had a personal interest in such donations (ovarian failure or surgical castration; group 2). This study of the general public’s views on ovarian tissue donation is concordant with the published views of ethics committees regarding posthumous gamete donation: that explicit prior written consent of the donor is advisable when donations are procured with the intention of creating life and in this particular survey, to allow fertilization or transfer of preembryos to cause a pregnancy. Because of the general lack of knowledge regarding the potential utility of posthumous ovarian donation for research or therapeutic purposes, surrogates would have a difficult time authorizing such a decision based on the above criteria without explicit written consent. In light of the rapid technological advancements in follicle/oocyte cryopreservation and maturation for physiological studies and potential clinical uses, it may be time to provide potential organ donors the opportunity to specify their desires regarding ovarian tissues when registering for organ donation.

References


Assisted Reproductive Technology Committee and University of Washington (1997) Policy guidelines: assisted reproductive technology (ART) policy for posthumous harvesting of sperm for the purpose of reproduction with the surviving partner.

Barber v Superior Court, California Court of Appeal, Second District (1983) 147 Cal. App. 3d 1006, 195 Cal. Rptr. 484.


Submitted on August 18, 2004; resubmitted on March 14, 2005; accepted on June 17, 2005