Human Reproduction, Vol.24, No.12 pp. 3144–3149, 2009
Advanced Access publication on September 3, 2009 doi:10.1093/humrep/dep309

human reproduction

ORIGINAL ARTICLE *Psychology and counselling*

US oocyte donors: a retrospective study of medical and psychosocial issues

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BACKGROUND: First-person reports of oocyte donors, years after their donation, can give valuable information about medical complications of oocyte donation, as well as changes potentially required in procedures and priorities of US-based *in vitro* fertilization (IVF) centers. This paper reports findings from an online survey of former oocyte donors.

METHODS: The instrument was an author-constructed questionnaire completed online on the Donor Sibling Registry website. Questions assessed women's accounts of medical complications, contact with the infertility clinic through which they had provided ova, and information exchange or contact with people conceived from their ova.

RESULTS: Responses were received from 49.1% of the 287 donors with valid e-mail addresses. The 155 respondents completed the survey an average of 9.4 years after their first donation. Reported medical complications included ovarian hypersensitivity syndrome (30.3%) and infertility (9.6%). Subsequent to ova donation, 2.6% of women reported that they had been contacted by the IVF clinic for medical updates. On the questionnaire, 34.2% of women reported that medical changes they thought would interest donor children; half said that they had attempted to report these changes to the clinic with variable results. Many, who did not report such information, did not realize they could or should. Donors said that they frequently had not sought information about pregnancy outcomes because of confusion about the definition of 'anonymity' or 'confidentiality'.

CONCLUSIONS: US-based IVF clinics need to give clearer guidelines to anonymous oocyte donors about follow-up information exchange. Additional long-term studies are needed to ascertain oocyte donors' risks of infertility or cancer.

Key words: long-term study / oocyte donors / informed consent / anonymity

Introduction

With the advent of safe and available birth control and reproductive options, more women have delayed having children until their late 30s and 40s. This has led to a large increase in demand for infertility services, with ~1% of US infants born in 2004 conceived through assisted reproductive technologies (ASRM, 2004). *In vitro* fertilization (IVF) programs are very available, and the technology and success rates with these procedures have greatly increased. These two factors, as well as demands from stem-cell research facilities, have created a large gap between the demand for and the availability of oocyte donors. To meet the demands for a limited resource, agencies and IVF programs in the USA are recruiting women by offering large sums of money to undergo an oocyte retrieval cycle, typically $8000–15 000 per cycle, but at times up to $100 000. Donors are recruited through the Internet, as well as posters and advertisements in newspapers on the campuses of major American universities. Several states are now considering paying oocyte donors for oocytes to be used in stem-cell research, and New York State voted in 2009 to do so. Many women choose to sell their oocytes primarily as a means of supplementing their income, and with the recent downturn in the world economy, the number of women in the USA pursuing oocyte 'donation' is growing.

It is estimated that 100 000 young women have sold or donated their oocytes to ~470 IVF clinics in the USA (Schneider, 2008) following one or more cycles of hormonally induced ovarian stimulation, or superovulation. After oocyte retrieval, they are discharged from the IVF clinic but are rarely contacted afterwards. Consequently, there has been a dearth of studies of even short-term adverse consequences of superovulation for oocyte donation. In one of the few such studies conducted (Jayaprakasan *et al.*, 2007), 14.5% of 339 infertile women undergoing ovarian stimulation required hospitalization for ovarian hyperstimulation

syndrome (OHSS). Another recent retrospective study of early complications of oocyte retrieval showed that 22 (1.1%) of 1917 oocyte donors experienced moderate-to-severe OHSS, with half requiring hospitalization (Bodri *et al.*, 2008). Because the hospitalizations in the former study occurred among younger women who grew numerous follicles, the authors recommend active monitoring during the first week after oocyte retrieval for oocyte donors who develop at least 20 follicles during a superovulation cycle.

Much less is known about long-term risks of ovarian stimulation and/or vaginal oocyte retrieval (Schneider, 2008). In the general population, the incidence of premature ovarian failure (POF) is 1 in 250 women by age 35, and 1 in 100 by age 40 (Coulam *et al.*, 1986; van Kasteren and Schoemaker, 1999). Reduced fertility in oocyte donors could theoretically result from a decrease in oocyte quality or quantity after repetitive ovarian stimulation, or from pelvic infections or adhesions. A study of oocyte quality and quantity after repeated ovarian stimulation in young, healthy oocyte donors found that five or fewer successive stimulation cycles did not impair ovarian response (Caligara *et al.*, 2001). No differences were found in fertilization, implantation and pregnancy rates according to the oocyte's cycle origin. In contrast, a progressive decrease in ovarian response was found in successive cycles in women with ovarian endometriosis (Al-Azemi *et al.*, 2000).

There is also a possibility of oocyte donors developing an immune response that would prevent or hinder fertility (Barbarino-Monnier *et al.*, 1991; Gobert *et al.*, 1992). The aspiration of numerous follicles and the multiple punctures through the ovarian capsule and stroma releases antigens that were previously 'unseen' by the woman's immune system.

Although there are no studies of the long-term effects of ovarian stimulation in healthy young women, there are several population studies on cancer risks in infertile woman treated with fertility drugs. The literature is mixed as to the cause/effect of gonadotrophin therapy and cancer in infertile women (Ness *et al.*, 2002; Althuis *et al.*, 2005; Brinton *et al.*, 2005; Brinton, 2007), but the number of papers that support this association is steadily growing. In a recent long-term population-based historical cohort study of parous woman, those who were given drugs to induce ovulation had an increased overall risk of cancer, especially uterine cancer following treatment with clomiphene (Calderon-Margalit *et al.*, 2009). Breast cancer, malignant melanoma and non-Hodgkin lymphoma risk was also more pronounced, especially in women who waited more than 1 year to conceive and thus received longer exposure to ovulation induction agents. An association between the use of ovulation-inducing agents and ovarian cancer was neither found in this study nor in a Danish cohort study of 54 362 women with infertility problems (Jensen *et al.*, 2009). However, the Danish study did find a significantly increased risk (67%) of serous ovarian cancer (a histological type that constitutes the majority of epithelial ovarian cancers) after the use of clomiphene. Whereas the authors of that study say that they found no evidence for a strong association between the use of fertility drugs and the risk of ovarian cancer, they pointed out that many of the women in the cohort had not yet reached the peak age for ovarian cancer and continuous monitoring was needed. Additional complications reported after ovarian stimulation include cases of stroke (Girolami *et al.*, 2007) and colon cancer (Ahuja and Simons, 1998; Schneider, 2008).

There have been few long-term studies of oocyte donors' motivations and expectations. A recent survey of 80 oocyte donors who were questioned 2–15 years after their first donation found that their awareness of risks did not match the physical side effects they experienced. In that study, 20% of donors were unaware of any possible physical risks before their first donation, yet 16% reported serious physical long-term conditions, including impaired fertility, ovarian cysts, fibroids and chronic pelvic pain, which they attributed to having donated oocytes (Kenney and McGowan, 2008).

In recruiting potential oocyte donors, fertility clinics in the USA tend to understate the medical risks (Gurmankin, 2001). Because the IVF clinic is financially connected to the recipient, there is a potential conflict of interest in having the clinic be the providers of informed consent to the donor, as it is in the clinic's best interest to present information as positively as possible. Even when known risks are fully discussed, and prospective donors are informed that long-term risks are unknown, they may not clearly understand the difference between 'there are no known risks' and 'there are no risks' (Schneider, 2008).

Because IVF clinics do not maintain contact with the oocyte donors, it is difficult to perform the studies necessary to obtain adequate data about any long-term risks, and to obtain information about the donors' feelings about their decision to donate, their experiences with the IVF clinic and what aspects of the donation process need improvement. Regarding the current policies in US fertility clinics about maintaining donor anonymity, several studies have indicated an interest by former oocyte donors in having contact with their genetic offspring (Fielding *et al.*, 1998; Kalfoglou and Geller, 2000; Patrick *et al.*, 2001; Braverman and Corson, 2002), and a recent review of published studies by Daniels (2007) concludes that the removal of anonymity for donors should be seen as part of a significant cultural change regarding assisted reproduction.

To answer some of these questions, we undertook a retrospective questionnaire study of former oocyte donors, many of them many years after oocyte retrieval. We chose a retrospective approach rather than the ideal prospective survey because the latter would have required a decade or more to collect the data. Our objective was to learn more about donors' experiences, medical outcomes, attitudes and feelings regarding their donations.

Materials and Methods

A questionnaire consisting of 25 directed and open-ended questions was constructed to produce both qualitative and quantitative data about oocyte donors' experiences, medical outcomes, attitudes and emotions regarding their donations (Table I). Questions were developed following discussions with several donors. The questionnaire design, including questions and response options, was informed by previous research carried out with donor conception families (Lycett *et al.*, 2005; Freeman *et al.*, 2009).

The questionnaire was available on the website of the Donor Sibling Registry (DSR), a US-based worldwide registry founded in 2000 that helps donor-conceived individuals search for and contact their donor and donor siblings (i.e. half-siblings), as well as supplying support, news and education for former donors, prospective donors and individuals interested in pursuing this option. At the time of this study, there were 287 women registered on the DSR website who had donated oocytes and had a valid e-mail address. Invitations to complete the survey were

Table I Survey questions (http://www.donorsiblingregistry.com/DSRblog/index.php)

1. What was your age at time of donations? Your age now?
2. How many donations have you done?
3. Do you have children of your own previous to your donations?
4. Have you had children of your own after your donations?
5. How long after your donations did you have children, if any?
6. Any complications during or following any of your donations? i.e. infection, hyper-stimulation, etc.
7. If any complications, what type of care, treatment, follow-up was required?
8. Do you know if any of your donations resulted in pregnancy, birth, etc.?
9. Have you asked your fertility center if there were successful births?
10. Any medical changes to your health or a close family member of yours that should be updated to your recipient if you could?
11. Have you noticed any change in your menstrual cycle, ovulation, own fertility since your donations?
12. Have you ever been contacted by your fertility center for any type of medical updates?
13. Have you attempted to contact your fertility center to update them on any medical issues?
14. Would you contact the fertility center if there were any medical or genetic updates that your donor families should know about? (If the answer is no, will you explain why not?)
15. Has anyone attempted to follow-up with you after your donations in relation to your donations themselves?
16. Would you be open to contact if it was requested? (of any level)
17. Do you have contact with any of your recipients? If so, what level of contact?
18. Do you feel that you were properly educated and counseled on the potential curiosities of the children to be born? (Many donor conceived people are curious as to their genetic heritage and wish to meet their donors.)
19. Is there anything you wish you had been informed of prior to your donations to better prepare you in making your decision?
20. Did you have any infertility issues before donating? If yes, please describe
21. Did you have any menstrual cycle problems before egg donation? If yes, please describe
22. Had you considered IVF before becoming an egg donor?
23. If yes, did you try IVF?
24. Did you donate eggs as part of egg sharing?
25. Did you have infertility problems after egg donating? If yes, please describe

e-mailed to all of them. Participants were required to log-in in order to access the questionnaire.

Results

Demographics

Responses were obtained from 155 of the 287 oocyte donors with valid e-mail addresses who were registered on the DSR (49.1% response rate). The demographics of this group are shown in Table II. Five women had undergone 12 oocyte retrieval cycles.

The nine respondents who had donated oocytes to help pay for their own IVF had infertility problems such as blocked Fallopian tubes, previous tubal ligation or polycystic ovary syndrome. At the time of data collection, 14 women (9.0%) had undergone their first donation cycle within the previous 2 years, and 80 of 155 women (51.6%) had performed oocyte donation over 10 years earlier.

Medical outcomes

Table III summarizes the reported immediate and long-term complications following oocyte donation. The most common immediate complication was OHSS: 47 (30.3%) reported some degree of OHSS, which in 18 (11.6%) required hospitalization and/or paracentesis. Several respondents reported that when they developed symptoms of OHSS shortly after oocyte retrieval, it was difficult to obtain medical follow-up at the IVF clinic, especially on the weekend.

Forty-one women (26.4%) reported new infertility and/or menstrual cycle changes following donation. Of the 15 women (9.6%) reporting a new infertility problem, only four became pregnant after donation, despite their attempts to conceive. One woman, who had a strong family history of breast cancer, was diagnosed with breast cancer at age 41, 12 years after her first oocyte donation; another was diagnosed with melanoma at age 35.

Information received from the IVF clinic

When asked 'Is there anything you wish you had been informed of prior to your donations to better prepare you in making your

Table II Demographics of survey respondents (n = 155)

Age at first donation (mean and SD)	26.4 (4.2) years; range 18–40
No. of egg cycles (mean and SD)	2.9 (2.4) range 1–12
% who bore children before donation	43.2%
% who bore children after donation	36.1%
No. pregnant at the time of survey	8
No. who had donated eggs to pay for own IVF	9
Age at the time of survey (mean)	35.8 years
No. of years since first donation (mean and SD)	9.4 (5.2) range <1 to 22 years

Table III Reported complications post-oocyte retrieval (n = 155)

Complication	Number (%)
Some degree of OHSS	47 (30.3%)
OHSS-related hospitalization and/or paracentesis	18 (11.6%)
Infertility and/or menstrual changes since donation	41 (26.4%)
New infertility problems (post-donation)	15 (9.6%)

decisions?', almost two-thirds of the respondents (63.2% or 98/155) replied negatively, indicating that they were satisfied with the information they received. The remaining 36.8% wished that they had received additional information on medical issues including side effects of ovarian stimulation, the risks of OHSS, contacting the clinic with health information and the potential long-term side effects from the oocyte retrieval and the medications taken, in particular infertility and cancer, as well as information on psychosocial issues such as anonymous versus open donation, possible emotional reactions, fate of other embryos, the possible need of future children to be in contact with their genetic half-siblings and the likelihood of half-siblings meeting. Looking back to the time when they donated the oocytes, 57 of the 155 respondents (36.7%) reported that they were properly educated and counseled on the potential curiosity of the children to be born.

Follow-up by IVF clinic

Only four respondents (2.6%) reported that their clinic had initiated contact with them to update their medical information. When asked if they had experienced medical changes of potential interest to oocyte recipients and offspring, 34.2% (53/155) of respondents answered affirmatively. Of these, 31 attempted to contact their fertility centre to update them. Several reported a negative outcome: a missing or destroyed chart; a clinic that had closed or relocated and could not be found; and a clinic that declined to notify oocyte recipients on the basis of anonymity.

On another question, respondents were asked whether they would contact the fertility clinic in the future to convey 'any medical or genetic problems that the recipient families should know of'. Of the 155 respondents, 103 (66.5%) simply said yes. Among the remainder, 13 said that they had not thought about it until asked; 4 wrote that they did not realize they were supposed to or were permitted to contact the clinic with information; 7 said that the clinic was closed or they could not contact it; 2 wrote that they were told their donations were anonymous or that any contact would not be welcome. Seven answered 'maybe'—only if they thought their medical problem was genetic or severe. The remaining responses included, 'Why worry the parents?' 'I doubt they'd tell the families anyway'. 'I had a full genetic screening at the time of donation, so there's no need'.

Information about pregnancies and births

When asked, 'Do you know whether any of your donations resulted in pregnancy, a birth, etc?', 77 (49.7%) of the 155 donors responded affirmatively. The most common source of this information was the fertility clinic, which at times volunteered information about successful births, at other times responded to the donor's query (see below); only one donor was told by the oocyte donor agency. In one case, the donation was open. Most of the remaining 78 respondents said that they did not know the outcome with certainty, although several inferred that there had been pregnancies because they were repeatedly asked to donate additional oocytes.

To the question, 'Have you asked your fertility center if there were successful births?', 76 (49.0%) of the donors replied 'yes', but only half of these had been provided with the information they sought. The others were often told that it was against the clinic's policy to release any information. Among the 49.7% of respondents who did not attempt to contact the clinic to learn about births (two did not reply), their most common reason was that they had been told initially that such information would not be available to them.

Effect of length of follow-up on oocyte donors' responses

To learn whether the elapsed time since oocyte donation might have influenced some of the respondents' perceptions of their experience, we divided the 155 responses into three groups: (1) 0–6 years since first donation ($n = 47$), (2) 6–11 years ($n = 48$) and (3) 12–22 years ($n = 60$). (To divide into the groups, the respondents were arranged in order of length of time since oocyte donation and then divided into three approximately equal groups.) For statistical analysis, the 2×3 table was broken down into three 2×2 tables, a Bonferroni adjustment was accordingly made, and χ^2 tests applied. A highly significant larger proportion of Group 2 than of Group 1 (adjusted χ^2 test $P = 0.010155$) and of Group 3 than of Group 1 (adjusted χ^2 test $P = 0.007509$) believed that they had not been properly educated on the potential curiosity of their children to be born. The responses of Groups 2 and 3 did not differ significantly. Thus, more women whose first oocyte donation was <7 years earlier felt that they were properly counseled than did those whose first donation was 7 years earlier or longer.

Group 3 members, whose mean age at the time of the questionnaire was 41.7 years, reported more health-related changes than did those in Group 1 (mean age = 29.1 years)—41.7% versus 25.5%, but this difference did not reach significance (χ^2 test P-value for a 3×2 table = 0.21524). When asked whether they wish they had been informed of anything else to better prepare them to make a decision, there were no significant differences between any of the groups (χ^2 $P = 0.919731$), with ~60% of the total respondents believing that they had received enough information to prepare them for the oocyte donation.

Discussion

This retrospective study surveyed 155 oocyte donors, 9.4 ± 5.2 years after their first donation (range <1–22 years), and detailed medical complications and subsequent health problems, contact with the IVF clinic, donors' satisfaction with the donation process and current feelings. Respondents were recruited from the DSR, a US-based registry that helps donor-conceived people search for their donors and vice versa. Reported medical complications included OHSS and infertility. Only 2.6% of survey respondents had been contacted by the IVF clinic for medical updates; 34.2% reported medical changes they thought would be of interest to donor children and half had attempted to report these changes to the clinic, with variable results. Many of those who did not report changes did not realize they could or should. Donors frequently had not sought information about the outcome of their oocyte donation because of confusion about the definition of 'anonymity' or 'confidentiality'.

The chief limitation of this study is that participants were recruited from a website that attracts those donors who wish information about their donor-conceived offspring (and vice versa). We cannot, therefore, extrapolate to the general donor population these respondents'

answers to questions about their desired contact with offspring (97.4% were open to such contact) or their wish for more information about their offspring. Because of this limitation, the discussion in this paper focuses on their remaining questions and answers (see Table 1), which provide information that would be of interest to reproductive medicine professionals. An additional limitation is that a retrospective study always has the possibility of inaccuracies in recall and memory.

Effects of ovarian stimulation

The results of the present study are in agreement with previous reports of the prevalence of OHSS following ovarian stimulation, now recognized as a common adverse effect (Jayaprakasan *et al*., 2007; Bodri *et al*., 2008). We found that 11.6% of respondents had required paracentesis and/or hospitalization for OHSS.

Secondary infertility has been reported following ovarian stimulation (Barbarino-Monnier *et al*., 1991; Gobert *et al*., 1992). In the present study, 16.8% of respondents reported some menstrual problems and 9.6% noted infertility problems. Since the mean time since first oocyte donation was 9.4 years, some of these changes may be unrelated to the oocyte donation. Similarly, most respondents had not attempted pregnancy before oocyte donation, which makes it difficult to determine the extent of prior unrecognized infertility problems. Another unknown is whether any miscarriages had any relation to the ovarian stimulation. Although the present study is not powered to draw statistical inferences about the risk of infertility in IVF, the preliminary data suggest an adverse effect of hormonal stimulation on menstrual cycle or fertility and increased risk of POF.

Clearly, ovarian hyperstimulation entails a significant degree of risk, which increases with the number of cycles undergone. Whereas five or fewer successive stimulation cycles do not seem to impair ovarian response (Caligara *et al*., 2001), the American Society of Reproductive Medicine (ASRM) cautions that the number of adverse events after a given number of procedures is additive and, therefore, recommends a maximum limit of six cycles of oocyte donation (ASRM, 2008). It may serve oocyte donors better to have more stringent recommendations. There is clearly a need for an oocyte donor registry that includes records of subsequent and prior fertility problems, and the number of cycles of oocyte retrieval undergone by the donor. This would permit prospective follow-up studies of fertility in oocyte donors after oocyte retrieval.

As for long-term risks for oocyte donors, only isolated case reports have suggested a possible cancer connection (Ahuja and Simons, 1998; Schneider, 2008). A large cohort with long-term follow-up, such as an oocyte donor registry, is needed to obtain meaningful data. In 2001, Caligara *et al*. recommended the establishment of a world registry for oocyte donors to detect both adverse effects of oocyte donation as well as assess long-term risks, such as an increased incidence of POF, ovarian cancer, or breast cancer. To date, no such data have been published.

Contact between fertility clinic and oocyte donor

One of the striking findings of this study is that only 2.6% of oocyte donors were contacted by the fertility clinic after their donation to update information that might impact the health of donor-conceived offspring. In our survey, respondents reported developing breast cancer, being diagnosed with hemochromatosis, or giving birth to a child who is a carrier of cystic fibrosis. Perhaps even more striking was the finding that over 40% of the oocyte donors who reported a new medical problem in themselves or a family member did not attempt to contact the fertility clinic. Overwhelmingly, the reason was lack of education about the value of providing such information, along with the lack of encouragement by the fertility clinic to do so. In the absence of clear guidance from the fertility clinic, most respondents did not think about contacting the clinic, or they planned to decide on their own if the information would have relevance. Some let their belief that there was insufficient concern for their well-being which prevents them from giving information that might benefit their offspring. Several oocyte donors who did attempt to contact the fertility clinic were unable to do so.

Recipients should be informed of any health-related changes in donors that could impact their offspring. Similarly, if the fertility clinic learns that any IVF-conceived children have been born with genetic abnormalities or potentially inherited diseases, it would be ethically imperative to notify the oocyte donor as it may influence her decision to provide additional oocytes or to have children of her own.

Information about pregnancies and births

In our study, approximately half of the oocyte donors knew whether any pregnancies or births had resulted from their oocytes. Of those who did not know and had attempted to find out, only half were given the information. Most oocyte donations in the USA are termed anonymous, but many oocyte donors are uncertain about what 'anonymity' means and whether information about the outcome of the donation would fall in the category of identifying the recipients or children.

As expected from the method of subject recruitment, the respondents in this study expressed a clear interest in the outcome of the oocyte donation and an overwhelming willingness to have contact with children. However, because of the method of subject recruitment, no recommendations can be generated from our findings.

In 2009, the Ethics Committee of the ASRM published a report outlining the interests, obligations and rights of gamete donors (ASRM, 2009). Their recommendations state that programs should respect the rights of donors to be informed about legal, medical and emotional issues involved in gamete donation, that medical updates be provided by donors and that information sharing about outcomes be facilitated.

Implementation of these and other excellent suggestions will require the establishment of new protocols in US fertility clinics. Only active advocacy by ASRM will make it likely that changes are implemented in a timely fashion.

Conclusions

The results of this study reinforce the need for increased attention to the health and safety of oocyte donors in the USA. IVF clinics should provide anonymous oocyte donors clear guidelines about requesting outcome information or giving the clinic medical updates to benefit their biological children. Additional long-term studies are needed to ascertain oocyte donors' risks of infertility or cancer. The recent

recommendations of the Ethics Committee of the ASRM are a significant step in the right direction; they need to be translated into clear guidelines that specify new policies in US fertility clinics.

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Submitted on April 28, 2009; resubmitted on August 8, 2009; accepted on August 11, 2009