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Advocating for longitudinal follow-up of the health and welfare of egg donors

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Egg donation continues to increase in popularity as part of assisted reproduction (1). Although short-term health effects of donation have been well studied, many unanswered questions remain about the long-term medical and psychological consequences for women who donate eggs. Studies of longer-term postdonation health effects have significant limitations, and are often retrospective, cross-sectional, or case studies.

In its 30-year history, egg donation has led to the birth of more than 200,000 children into previously infertile families. Among fertility clinics in the United States, 93% offer egg donation (1). Donor eggs are most often used by women over the age of 40 years, as their in vitro fertilization (IVF) success rates are greater when using donor eggs (49.4%–50%) compared with their own (0.0%–23.6%) (1). As more women and couples find themselves delaying parenthood to pursue careers or education, donor eggs are becoming an increasingly important component of assisted reproductive technology (ART) for women of advanced reproductive age.

The increased use of donor eggs raises questions regarding the long-term medical and psychological effects of egg donation. In the great majority of egg-donation cases, certainly in the short term, donors seem neither to be harmed (2) nor to regret having participated (3). Yet, anecdotal testimonies of donors who feel that they were harmed by going through the process have appeared in the media, outside of medical journals. Hence, understanding all potential risks faced by donors is important. Prospective donors cannot make truly informed decisions without knowing all the risks. Donation may have only minor medical or psychological consequences, but more data are needed to ensure fully informed consent and possibly to protect donor health.

Two previously proposed ways (4) to better characterize the egg-donor experience are creation of a mandatory national egg-donor registry, and voluntary participation in fertility

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clinic–driven registries and/or data collection. Yet, these methods have not been implemented, and the advantages and disadvantages of these or other approaches has not been systematically considered with respect to egg donors. This article provides an examination of the short-term and long-term risks of egg donation and describes 3 possible means of responding to gaps in current knowledge. Specifically, the pros and cons of 2 past proposals are examined, and a third approach is suggested: a government-funded prospective long-term multicenter follow-up study of egg donors to systematically examine long-term safety and health risks.

PAST STUDIES AND LIMITATIONS

We review below short- and long-term medical effects and long-term psychological effects of egg donors.

Short-Term Medical Effects of Egg Donation

The short-term medical risks of egg donors probably mirror those of the general IVF population, as donation and IVF have similar methodologies, including ovarian stimulation and oocyte retrieval. However, unlike infertile recipients, egg donors presumably face a different reproductive future, and therefore potentially different long-term risks. Although many studies report on short-term effects in infertile populations, fewer studies examine egg-donor populations specifically.

Short-term risks of egg donation include ovarian hyper-stimulation syndrome (OHSS) (0.38%), intra-abdominal bleeding, infection, ovarian torsion (2), and short-term subfertility (5%–10%) (5). Serious complications seem to be rare (<1%) (2). Despite the fact that egg-donation and IVF methodologies have similarities, egg donors are not infertile, and they are socioeconomically and demographically distinct. Hence, focusing only on immediate measures of safety (e.g., risks of anesthesia, bleeding, infection) and generalizing from data gathered within the IVF population to egg donors is inadequate.

Long-Term Medical Effects of Egg Donation in Egg-Donor Populations

Less is known about the long-term medical consequences of egg donation. Little evidence either supports or denies possible concerns about the effects of donation on future fertility. Few studies have examined the long-term medical effects of egg donation, such as fertility, cancer, and other potential health risks, and each study has had methodological shortcomings and varying lengths of follow-up (Table 1).

Four survey-based studies have looked at the long-term postdonation health of egg donors. In a telephone survey of donors, averaging 4.5 years postdonation, 5% of respondents later required fertility treatment (5). A second study, with a slightly longer average length of follow-up found that, postdonation, 9.6% of participants reported new infertility issues, and 26.4% reported fertility and/or menstrual problems (5). In a third retrospective study with a slightly longer follow-up period (2–15 years), 16.3% of participants attributed physical symptoms (e.g., infertility, cysts, fibroids, and weight gain) to having donated their eggs, and 20% of participants reported long-term psychological effects related to donation (3). In the fourth study, surveying non-paid donors, 15% of donors experienced minor gynecological issues 12–18 months later (6).

Yet, these 4 studies have significant limitations, such as relying on self-reported data (introducing the possibility of significant bias), and using a small sample size. Additionally, the follow-up times were not long enough to identify sufficiently long-term medical and psychological risks, as some of the women surveyed had donated only 1 to 2 years before taking the survey (3, 5, 6). The first study recruited participants from a single donor agency, limiting the generalizability of the results, and given its retrospective cross-sectional design, the data collected provide little information about the cause of reported psychological and medical issues (i.e., any possible relationships between donation and later medical and psychological problems) (5). The prevalence of infertility and subfertility found in these studies is also similar to that in the general population. Thus, it remains unclear whether the reported health problems women experience postdonation are related to their egg donation or represent baseline rates within the general population.

Long-Term Medical Effects in Non–Egg Donor Populations

Infertile women who underwent IVF have been the subject of more long-term study than have egg donors. Although egg donation and IVF have technical similarities, questions remain about the generalizability of information between these groups. Multi-decade follow-up studies have looked at the long-term effects of ovarian-stimulating drugs, particularly whether these drugs carry an increased risk for reproductive cancers. These studies have not found convincing evidence of an increase in ovarian cancers (2). However, these studies were conducted with non–egg donor populations, so whether the results are generalizable to egg donors is questionable. Infertility itself is a strong confounding variable for developing reproductive cancer (2). Research to date thus has limitations, notably the investigation of infertile women instead of fertile egg donors to assess risks.

Long-Term Psychological Effects of Egg Donation in Egg-Donor Populations

Little is known about psychological problems that may develop among egg donors after participation. Anecdotally, most women have positive experiences with egg donation; however, it is unclear if psychological issues, such as depression or anxiety, linked to participation manifest themselves in the long term. Although few women seem to regret their decision to donate, many former egg donors express dissatisfaction with their experience (3). Donors may encounter psychological issues about having genetic progeny in the world (usually being raised by parties unknown to the donor) and the difficulty of having contact with these children. For some women, other life experiences, such as later infertility, not necessarily related to their egg donation, may color these feelings. How women, whether satisfied or regretful about donation, cope with and relate to reproductive or other medical problems in the decades after egg donation is unknown. Thus, clinicians are poorly equipped to inform prospective egg donors about potential psychological risks.

Overall Limitations

Although cross-sectional and retrospective studies have been conducted, no longitudinal prospective studies published to date have addressed cancer risks, fertility, and other long-term medical and psychological issues among egg donors. To our knowledge, no meaningful long-term surveillance has been conducted related to medical or psychological issues felt by donors. More-robust data are thus needed to determine whether prospective egg donors should be informed about minimal long-term risks and complications in considering these procedures. A well-designed cohort study would permit exploration of any such problems that may develop over time.

POSSIBLE SOLUTIONS

Knowledge of health care risks for egg donors can be improved in 3 ways (Table 2). The pros and cons of each are presented below.

Solution 1: A Mandated National Egg-Donor Registry

A national egg-donor registry has been previously proposed (4), which could assist future research and permit short- and long-term follow-up of donors and any medical, psychological, or sexual problems. A national registry could also examine a larger sample than a longitudinal cohort study, and potentially provide a structure for regulatory oversight of egg donation (e.g., regarding individual donation limits). But a registry may be difficult to establish, given questions about what organization(s) would administer the registry and who would have access to the data (e.g., identity of participants). Donors often donate at a young age (20–30 years) and then relocate, and they may not consent to lengthy follow-up. Additionally, a registry that required collection of identifying information would potentially deter prospective donors from providing eggs, decreasing the availability and accessibility of ART and encouraging medical tourism to other countries.

Health care providers and fertility clinics may perceive a national donor registry to be an expensive bureaucratic burden. Moreover, it would increase the costs of ART—an already expensive medical undertaking. Fertility clinics are neither required nor incentivized by state or federal regulations to track donor health postdonation, and they generally do not. Hence, this data collection would add to provider and clinic responsibilities, until a system or funding is established to support it. To generate reliable and accurate data to determine risks of egg donation, a registry should include both clinic and donor data.

Solution 2: A Voluntary Egg-Donor Registry

An alternative to addressing these formidable challenges is to establish a voluntary registry. This type of registry could be anonymous and voluntary for both patients and clinics, maintain long follow-up periods, and have strict privacy protections and limited access to stored identifying data. The Infertility Family Research Registry (IFRR) (http://www.ifrr-registry.org/) may offer a useful model for such a system. Currently funded by the American Society for Reproductive Medicine (ASRM), the Dartmouth-based IFRR collects information on the overall health and reproductive history of individuals— classified as either fertile, infertile, egg or sperm donor, or carriers/surrogates—who voluntarily join the registry.

Few individuals have access to the data collected by the registry, and for additional confidentiality, data are encrypted and protected behind a secure firewall. The IFRR does not include fertility clinic data, but rather collects data from individuals who voluntarily register. A national egg-donor registry could be similar, but could be administered on a larger scale and allow fertility clinics to participate. For instance, such a registry could be regulated by an overarching governmental organization—e.g., the Centers for Disease Control and Prevention (CDC)— not a university medical center, and local fertility clinics in each state could contribute data. Indeed, the CDC, in conjunction with the Society for Assisted Reproductive Technologies (SART), now collects, maintains, and disseminates data from over 90% of US fertility clinics on over 150,000 ART cycles per year (1). Several questions arise as to who would agree to participate in a voluntary registry, whether it would be voluntary for both patients and clinics, and how long the follow-up would be. A voluntary and anonymous egg-donor registry would impose fewer regulatory restrictions on providers and clinics than a mandatory one, and would entail less administrative burden on the overseeing governmental agency.

Yet, a voluntary registry does not entirely avoid the pitfalls of a mandatory registry, and even presents new obstacles. Patients and providers may be concerned about privacy (i.e., whether information is available to a wide range of individuals, including providers, government agencies, and donor offspring). Hence, many egg donors and clinics may avoid participation, biasing the sample. Such self-selection bias may jeopardize the quality of the data, depending on what donors agree to participate. Moreover, no cohort would be available to compare with these women. Thus, the data would be less comprehensive and meaningful than those collected through a mandatory registry. Although these registries are promising, both types have substantial obstacles concerning compliance, privacy, regulation, and cost.

Solution 3: Funding a Longitudinal Follow-Up Study

Given the need for reliable data, but also the logistical, ethical, and regulatory obstacles to both mandated and voluntary registries, a third option is a multicenter longitudinal cohort study, funded by the National Institute of Child Health and Development or another National Institutes of Health (NIH) institution. The need for funding prospective studies of egg donors to obtain data on the long-term fertility and cancer risks of egg donation has been mentioned by others (3) but not comprehensively considered, with its merits weighed against other options.

To define any specific long-term risks of egg donation and make sense of longitudinal data requires a robust cohort study of age-matched controls. We could then understand if participation in egg donation is causally related to any future medical and psychological problems. The data generated from a well-powered longitudinal cohort study would be far superior to data collected from either a voluntary or mandated registry. Such a study may require more central funding than a national registry but have fewer administrative and personnel costs to individual clinics. The study could have more privacy and confidentiality protection, with information seen only by researchers. Large academic groups doing egg donation, if properly funded, could organize and administer a study of sufficient scale, providing the necessary institutional structure and stability. Academic groups would likely be less biased than private practices and fertility clinics because the former do not “own” the practice, and rigorous IRB and compliance oversight would occur. Also, in these academic institutions, any turnover of personnel who manage and maintain the databases would not threaten the study.

This option also infringes least on patients and doctors; and provides informed consent to each participant, and providers and clinics have the least reporting burden. Donor follow-up may be more successful than with a registry. Patients may relocate during the course of the study, but they could be contacted at regular intervals by the research team, and would have explicitly consented to such on-going follow-up. The cohort data collected, although from a smaller sample than a registry, could also be used for future research on egg donation.

A prospective study can take decades before providing clear conclusions on the long-term medical and psychological effects of donating. However, this time frame will be similar to, if not shorter than, that of a national registry, given the latter’s administrative, political, and practical hurdles. Although a large, multicenter cohort study with a decades-long follow-up period will require a relatively large monetary and time investment, NIH has funded other such studies. Infrastructure support offered by established academic institutions can sustain a study of this scale and ensure the longevity needed for on-going collection of valuable data.

CONCLUSIONS

Questions remain about the long-term medical and psychological health of egg donors. The negative impact does not appear very high overall, but it is nonetheless present and remains in urgent need of study, given the increasing incidence of donation. Donation is unique as a medical procedure, and extrapolations made from the infertile population may not be wholly applicable to characterize risks adequately. Hence, collection of these data is vital. The current state of uncertainty about risks to women who donate eggs creates problems, impeding women’s ability to make optimally informed decisions about whether to undergo this procedure. A national egg-donor registry, whether mandated or voluntary, can help fill gaps in the literature, but poses limitations and obstacles. Hence, a government-sponsored longitudinal follow-up study of egg donors is needed. Details would have to be determined, but it has the potential to improve understanding of risks incurred by egg donors and thus aid women’s health.

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TABLE 1

Summary of reports on long-term medical and psychological consequences of egg donation.

Author, year (reference)	Sample	Relevant findings	Length of follow-up period	Limitations/comments
Stoop, 2012 (5)	194 former egg donors	5% of donors needed fertility treatment postdonation	Average of 4.5 y after first donation (standard deviation: 2.3)	Cross-sectional telephone survey (measuring incidence, not cause-and-effect relationship)
Kramer, 2009; Stoop, 2012 (5)	155 former egg donors	9.6% of donors experienced new infertility problems postdonation; 26.4% reported infertility and/or menstrual changes postdonation	Average of 9.4 y after initial donation, ranging from <1 to 22 y	Retrospective study, survey (self-reported medical information); participants completed questionnaire on Donor Sibling Registry website (selection bias)
Kenney, 2010 (3)	80 former egg donors	16.3% experiencing physical symptoms (infertility, cysts, fibroids, weight gain) attributed to donation; 20% reported donation resulted in lasting psychological effects	2–15 y	Retrospective, self-report, small nonrepresentative sample size
Söderström-Anttila, 1995 (6)	27 former egg donors	15% reported minor medical issues postdonation; no emotional or psychological side-effects postdonation	12–18 mo	Retrospective, small sample size; subjects recruited from a single IVF clinic; unpaid donors; non-US donor sample

Woodriff. Needs for long-term study of egg donors. Fertil Steril 2014.

TABLE 2

Pros and cons of possible means of obtaining long-term follow-up data on egg donors.

Option 1: national egg-donor registry	
Pros	**Cons**
Enables short- and long-term follow-up of egg donors Has a larger sample size than a research study Provides structure for regulatory enforcement (e.g., individual donation limits) Protects donors against fraudulent practices by clinics and providers	Increases the cost of ART Increases regulatory and administrative burden for government, providers, and clinics May deter individuals from donating (decreasing the availability of eggs for ART and encouraging medical tourism) May generate backlash from providers/clinics who perceive registry as burdensome May make long-term follow-up of donors difficult (relocation since donating, no desire for contact) Increases likelihood of breaches of confidentiality and privacy as more individuals have access to donor information Infringes most on patients, clinics, and providers
Option 2: voluntary egg-donor registry	
Pros	**Cons**
Enables short- and long-term follow-up of egg donors Has a larger sample size than a research study Infringes less on providers and clinics than mandatory registry Lessens administrative burden compared with a mandatory registry given fewer participants	Increases the cost of ART May skew the sample due to selection bias Decreases ability to enforce regulations with lack of universal participation May make long-term follow-up of donors difficult (relocation since donation)
Option 3: funding longitudinal follow-up study	
Pros	**Cons**
Enables collection of data on long-term risks of egg donation superior to those in both kinds of registries Reduces costs (personnel and administrative) compared with a mandatory registry Can provide stronger confidentiality and privacy protections for donors Facilitates follow-up, because donors consent and have regular contact Infringes least on donors, providers, and clinics	Requires a large time investment for completion Creates no explicit opportunity for regulatory oversight (e.g., individual donation limits) May cost more than a registry Has a smaller sample size than a registry

Woodriff. Needs for long-term study of egg donors. Fertil Steril 2014.