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# Donor eggs for the treatment of infertility

Using donated eggs can be a remarkably successful fertility treatment in the right circumstances. Though donor egg pregnancies may carry some increased obstetrical risks, the risks are manageable and can offer women a chance at pregnancy when there is no other option.

**ABSTRACT:** Egg donation is a common treatment for infertility. It is most often used for women with premature menopause, advanced reproductive age, or a history of unsuccessful in vitro fertilization attempts. Because egg donors are generally in their 20s, pregnancy success rates are high. In many cases, donor eggs give women a chance at pregnancy when there would be no other option. Donor egg pregnancies may carry some increased obstetrical risks related to preeclampsia and advanced maternal age. Community physicians are well positioned to counsel women on donor eggs as well as to care for women with a donor egg pregnancy.

## Background

Egg donation involves using eggs from a fertile woman to create a pregnancy in an infertile woman by means of in vitro fertilization (IVF). The woman receiving the egg will not be genetically related to the child but will be considered the birth mother.<sup>1</sup>

The first birth from a donor egg was reported in 1984, and the egg was fertilized in vivo.<sup>2</sup> An anonymous egg donor was inseminated, and then uterine lavage was performed at precisely

the right time to recover the resulting embryo, which was transferred into the intended mother's uterus.<sup>2,3</sup>

In the early 1980s, assisted reproductive technology was developing rapidly in Canada and around the world.<sup>4</sup> Fertility pioneers used laparoscopy to retrieve donor eggs for fertilization in vitro.<sup>3,5,6</sup> These early "third-party reproduction" techniques were groundbreaking at the time, given that the world's first IVF baby, Louise Brown, had been born in 1978.<sup>7</sup>

Today, the use of donor eggs is an increasingly common fertility treatment.<sup>8</sup> According to the Canadian Fertility and Andrology Society, some form of donor eggs were used in more than 10% of all fertility treatment cycles in 2018. Their use nearly doubled in 5 years: 3055 cycles involved donor eggs in 2018 compared with 1587 treatment cycles in 2013.<sup>9</sup>

## Indications for donor eggs

The indications for donor eggs include advanced reproductive age, diminished ovarian reserve, poor oocyte or embryo quality in prior attempts at IVF, hypothalamic hypogonadism, and the possibility of passing on a significant genetic defect. In practice, the most common indication is age-related fertility decline. Often, a woman's choice to use donor eggs comes after failed attempts at IVF with her own eggs. In these cases, donor eggs offer a chance at pregnancy when there is no other option.

Advanced female age is an increasingly prevalent cause of infertility. Women are waiting until later in life to have children. British

Columbia has the highest age of first birth in Canada at 30.5 years versus 30.3 years in Ontario.<sup>10</sup> According to Statistics Canada, 2010 marked the first time that more women in their 30s were having children compared to women in their 20s.<sup>11</sup>

The possible consequences of delaying childbearing are infertility, embryo aneuploidy, and miscarriage. These are largely attributed to aging oocytes with failing meiotic spindles and other ooplasm deficiencies such as mitochondrial dysfunction.

Unlike sperm, which are constantly regenerated by the billions in a 70-day cycle,<sup>12</sup> eggs are not replenished. Women are born with all their eggs. A female attains her lifetime maximum number of oocytes, 6 to 7 million, around 20 weeks gestational age in utero.<sup>12</sup> By puberty she has about 300 000 oocytes remaining, arrested in primordial follicles at the diplotene stage of meiosis 1.<sup>13</sup> The eggs stay dormant and continue to age with the woman until they become hormonally responsive for 14 days during a menstrual cycle. At ovulation, half the chromosomes are supposed to migrate into the first polar body. When the egg is fertilized, the sister chromatids separate and half of them should end up in the second polar body. If either division does not occur correctly, aneuploidies such as trisomy or monosomy are the result. Older eggs are much more prone to errors. A 41-year-old woman undergoing IVF should expect nearly 70% of her embryos to be aneuploid compared to just over 20% in a 29-year-old woman.<sup>14</sup> At age 44, almost 90% of a woman's embryos would be

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expected to be abnormal, and live birth rates, even with IVF, are less than 2%.<sup>15,16</sup> Conversely, advancing paternal age has not been associated with higher miscarriage risk when studied in an egg donor cycle.<sup>17-19</sup>

Aneuploidy rates, combined with physiological decline in ovarian reserve, are the main reasons pregnancy can be difficult to achieve in women of advanced reproductive age. Hence, when it comes to the problems of poor egg quality or early menopause, donor eggs are a cure for the incurable.

Donor eggs are not exclusively for infertile women. They are also important for same-sex male couples and single men who lack the requisite gamete. These situations also require a uterus to gestate the pregnancy, which can take one of two forms. When the woman donating the egg is also the one to carry the pregnancy, it is referred to as *traditional surrogacy*. In contrast, a *gestational carrier* is a woman who carries a pregnancy derived from an egg that is not her own (i.e., she is not genetically related to the fetus).<sup>20</sup>

Lesbian couples or trans men can undergo “directed” egg donation, whereby eggs from one partner are used to create an embryo for the other to carry. Reciprocal IVF, or “egg-sharing” as it is commonly called, is usually performed in a similar fashion to traditional IVF.

This article focuses on anonymous frozen donor eggs, which are currently the most prevalent type of egg donation.<sup>3</sup>

### Donor eggs in fertility treatment

The most accessible source of donor eggs for Canadians is a frozen donor egg bank in the United States. Clients (aka intended parents) browse online profiles of donors, which include photos of the donor as a child and/or adult, a personal statement, her medical history, and genetic carrier screening results.

Prior to the existence of commercial frozen donor egg banks, patients had to find an altruistic family member or friend to act as a fresh egg donor. The donor would then undergo IVF at a local fertility clinic, which was often synchronized with the intended mother’s menstrual cycle to accommodate a fresh embryo transfer. The challenges of finding and coordinating altruistic donors could be burdensome and, in

many cases, prohibitive. In Canada, compensation for gamete donation and surrogacy services is regulated by federal law under the Assisted Human Reproduction Act.<sup>21</sup> Donations made in Canada must be altruistic, meaning that only out-of-pocket expenses can be reimbursed. New regulations made under the Act came into force in February 2020; they further specify the types of reimbursements that egg donors may receive.<sup>22</sup> The penalty for contravention of the Act is up to 10 years in prison and/or a \$500 000

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fine. These laws were designed to limit the exploitation of women’s reproductive capacity for profit,<sup>23</sup> but one consequence is that donor sperm and egg banks in Canada are almost nonexistent. Hence, most donor eggs used in Canada originate from Americans.

The American Society for Reproductive Medicine (ASRM) has published an Ethics Committee opinion that justifies financial compensation of donors in the US.<sup>24</sup> The logistics of obtaining frozen donor eggs are similar to those of frozen donor sperm, which has been a thriving industry in the US since the 1970s.<sup>25</sup> Frozen donor sperm was available nearly a half-century before frozen donor eggs, probably because of the ease of obtaining a sperm sample and the huge biological redundancy in the number of sperm per sample. The first pregnancy from frozen sperm was reported in 1953.<sup>25</sup> Comparatively, the use of frozen donor eggs has become popular in Canada only over the past 5 to 8 years. The technology for freezing eggs successfully took much longer to develop than for sperm, in part because of an egg’s fragile nature. The female egg (ovum) is the largest cell in the human body. Spherical and composed largely of water, the egg is vulnerable to ice crystal formation, which can damage the lipid membrane, microtubules, and meiotic spindle

during freezing–thawing. For years, the embryo freezing technique called “slow freezing” was adapted to eggs, with little success. In 2004, however, changes in Italian reproduction laws made it illegal to freeze embryos, which left clinics with no other option but to cryopreserve supernumerary eggs.<sup>26,27</sup> Those laws sparked the development of a new, more efficient method of “flash-freezing” eggs, called vitrification.<sup>26,28</sup> The technique uses ultra-rapid cooling rates and high concentrations of cryoprotectants to preserve the eggs in liquid nitrogen.

Vitrification proved so effective that in 2012 the ASRM removed the “experimental” label from egg freezing. Shortly after, the ASRM published a guideline stating that, in summary, frozen eggs work as well as fresh ones.<sup>29-31</sup> That guideline reviewed four randomized controlled trials, two of which involved egg donor/recipient cycles and the other two involved infertile couples with supernumerary oocytes after IVF. Egg freezing was performed using vitrification. Egg survival rates after freezing ranged from 90% to 97%, and fertilization rates after intracytoplasmic sperm injection (ICSI) were 71% to 79%. The clinical pregnancy rates ranged from 36% to 61% and were not significantly different than pregnancy rates with fresh eggs.<sup>29</sup> The guideline also stated that “Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population.”<sup>29,30,32</sup> Subsequent studies, including one analysis of 105 517 fresh autologous cycles compared to 2223 frozen donor egg cycles, have confirmed that success rates of frozen donor egg are equivalent to those of fresh eggs.<sup>31,33</sup>

In 2018, the Canadian average pregnancy rate for the first donor egg embryo transfer was 48%.<sup>9</sup> Because reproductive aging affects mainly a woman’s eggs and not her uterus, donor eggs from women in their 20s provide consistent pregnancy rates regardless of the recipient’s age group. For example, the 2018 Canadian data revealed an average success rate of 50.0% per embryo transfer in women younger than 35 years, and 47.4% in women 43 to 50 years of age.<sup>9</sup>

The proven efficacy of frozen eggs led to a substantial increase in social egg freezing for

women wishing to delay childbearing. It also paved the way for commercial egg banks to recruit healthy young women to donate their eggs for purchase by infertile women.<sup>33</sup> The compensation paid to donors varies widely in the US and internationally, ranging from US\$5000 to US\$10 000 per donation. The ASRM guideline states that compensation should be a reflection of the donor's time, discomfort, and inconvenience, and not proportionate to the number of eggs obtained.<sup>24</sup> Although US egg banks do not publish their average number of eggs retrieved per egg donation cycle, obtaining 10 or more eggs per cycle is likely a reasonable estimate.<sup>33</sup> Repetitive egg donation does not reduce serum levels of anti-Müllerian hormone, which is a validated marker of ovarian reserve. This has been taken to indicate that egg donation does not lead to premature depletion of a donor's ovarian reserve, even after five cycles.<sup>34</sup>

Egg banks typically sell frozen eggs in lots of six. The total cost to the patient for donor eggs, including the creation and transfer of embryos, is usually \$20 000 or more, depending on the egg bank and fertility clinic.

### Pregnancy considerations after donor egg IVF

The protocol for IVF with donor eggs is very similar to that of a frozen embryo transfer. The intended mother (recipient) is prescribed exogenous estrogen (17 $\beta$  estradiol tablets), which both stimulates endometrial growth and simultaneously suppresses her natural cycle of folliculogenesis and ovulation. Having a normal menstrual cycle is not a prerequisite, however, because even in menopause the endometrium will grow in response to estrogen. Once a sufficient endometrial thickness is confirmed by transvaginal ultrasound (usually after 14 days), the woman is instructed to start transvaginal progesterone; this simulates a luteal phase and prepares the endometrium for implantation. Simultaneously, the donor eggs are carefully thawed in the embryology laboratory, and each is injected with a single sperm from the intended father. Therefore, a future genetic test would show that the child is biologically related

to the father but not to the birth mother. (It is also possible to fertilize donor eggs with donor sperm for single women or in the case of male infertility.) Embryo transfer occurs after 5 days of development, at the blastocyst stage, when the embryo is almost ready to hatch and adhere to the appropriately synchronized endometrium. If a pregnancy results, it is essential that the woman remain on progesterone because the placenta does not start to produce it until

7 weeks gestation or later.

Egg donation pregnancies may have some increased risks. Egg donor recipients tend to be older. Although there is no law governing the up-

per age limit, Canadian clinics generally allow embryo transfer up until age 50, while the American guideline extends to age 55.<sup>35</sup> Fertility care providers should consider a multidisciplinary approach to preconception planning for women over 45 years of age. This may include the family physician, obstetrical internist, maternal fetal medicine specialist, and other members of the patient's health care team. The list of additional screening considerations can be individualized to each patient but may include screening for cardiovascular disease, diabetes, and mammography (which might otherwise be delayed by a year or more due to pregnancy and lactation). The Canadian Fertility and Andrology Society guideline also recommends that all couples who are using donor gametes should undergo assessment by a psychologist who is experienced in third-party reproduction counseling.<sup>35</sup>

Independent of age, egg donor pregnancies also appear to be at higher risk of gestational hypertension and preeclampsia.<sup>36-40</sup> In a large comparative cohort study, 217 egg donation pregnancies were matched for age with 363 autologous egg pregnancies. Pregnancy-induced hypertension occurred in 17.8% of the egg donor group compared to 5.3% of the autologous egg group ( $P < .001$ ).<sup>38</sup> Preeclampsia was also more common in the egg donor group (11.2%) than the autologous group (2.8%,  $P < .001$ ), and eclampsia was not recorded at all in the autologous group, whereas there were three cases (1.8%) in the egg donor group ( $P < .05$ ).<sup>38</sup>

The proposed pathophysiology is an immunologic intolerance between the mother and fetus leading to placental maladaptation.<sup>37</sup> In one systematic review of egg donor pregnancies, the authors explored the possible placental pathologies related to adverse pregnancy outcomes such as preeclampsia. They noted that egg donor pregnancies are different from solid organ transplant, as any pregnancy must be able to survive in a semi-allogeneic environment. Pregnancy itself requires a "complex interaction between hormones, cytokines, immune and nonimmune cells [to permit] fetus tolerance."<sup>37</sup> Egg donor pregnancies may require a higher degree of downregulation from the maternal immune response to allow for more mismatches in the human leukocyte antigen system.<sup>37</sup>

Conversely, it has also been proposed that the increased preeclampsia risk in donor egg pregnancies may be attributable to confounding risk factors. Despite statistical techniques to control for covariates, it is possible that advanced reproductive age, the baseline patient characteristics that necessitated IVF, or even the use of IVF itself cannot be adequately separated in studies on donor egg pregnancies.<sup>37</sup> In vitro fertilization is also associated with multiple pregnancies, which are well known to be higher risk.<sup>41,42</sup> A pilot randomized clinical trial attempted to compare pregnancy rates and twin rates after elective single embryo transfer versus double embryo transfer of embryos made from donor eggs. The study was terminated early when the authors found that both groups had an equally high cumulative pregnancy rate (73.5% single embryo, 77.4% double embryo), but the double embryo group had a 47.7% twin rate.<sup>41</sup> Fortunately, the current clinical trend is heavily in favor of single embryo transfer for egg donation cycles, specifically to avoid the risk of multiple gestation.

Obstetrical care providers should continue to offer prenatal screening to women with donor egg pregnancies. Most types of prenatal screening are valid in this setting, including integrated prenatal screening, serum integrated prenatal screening, first-trimester screening, and the quadruple marker screen.<sup>43</sup> The requisition will often request the birth date of the egg donor because a test's positive predictive value varies with the prevalence of

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a given disorder. Noninvasive prenatal testing, which sequences fragments of placental DNA circulating in the woman's blood, can also be used for donor egg pregnancies. Most commercially available brands of noninvasive prenatal testing are valid in singleton donor egg pregnancies. Twin donor egg pregnancies contain too many DNA profiles for some single nucleotide polymorphism microarray platforms. Advice from a genetic counselor may be required to select the appropriate type of noninvasive prenatal testing in donor egg pregnancies of multiple gestation.

### Summary

Egg donation is a fertility treatment that is quickly rising in popularity. The most common indications are premature menopause, advanced reproductive age, or previous unsuccessful IVF cycles. Frozen eggs are typically shipped in lots of six from commercial egg banks in the United States. Each egg is fertilized with a single sperm from the intended father, which means that the resulting offspring will be genetically related to the father but not the mother. Donor egg pregnancies may carry some increased obstetrical risks such as preeclampsia and those related to advanced maternal age. Obstetrical care providers should continue to offer appropriate prenatal screening to women with donor egg pregnancies. ■

### Competing interests

Dr Dunne is a member of the *BCM/J* Editorial Board but did not participate in the review or decision making regarding this article. No competing interests have been declared.

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