

## Who benefits from putting family life into ice?

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The first methods for fertility preservation (FP) were sperm freezing followed many years later by ovarian tissue freezing and oocyte vitrification. FP before cancer treatment is necessary because gametes are often destroyed at the same time as the cancer therapy kills malignant cells. It has been regularly offered to male cancer patients in the form of sperm cryopreservation. In female patients, slow freezing of ovarian tissue containing the oocytes was initiated in 1996 (1). It has since then been used for hundreds of young women, and after re-transplantation of the tissue back to the woman's ovary after her cancer treatment tens of healthy children have been born (2). There are also genetic disorders in which FP is needed, such as Turner syndrome (3). Ovarian tissue has to be biopsied under general anaesthesia. But getting mature oocytes instead of tissue is a simpler procedure. Oocytes are picked up using trans-vaginal ultrasound-guided needle aspiration after the woman's hormonal stimulation, which is routine procedure for *in vitro* fertilization (IVF). Ovarian tissue freezing is the only method available for pre-pubertal girls, but it is not needed for age-related decrease in fertility.

Human sperm has been frozen for about 60 years with the aim to use it later on for having children. Spermatozoa are very small cells, and it was technically relatively easy to cryostore them. But human eggs, oocytes, are very large cells. The diameter of a mature human egg is 120 µm. They are extremely sensitive to damage during freezing. But cryostorage of human eggs has also become feasible. The first attempts, using the conventional slow freezing method with dimethylsulphoxide as the cryoprotectant, were successful already 30 years ago and resulted in pregnancies and births (4,5), but the efficacy was low. The main cause of damage in slow freezing of cells is that ice crystals break intracellular organelles and cellular membranes. Vitrification is a cryostoring method in which low temperatures are achieved by adding high concentrations of cryoprotecting substances that form a glass-like amorphous mass when cooled to subzero temperatures. Hence, dangerous sharp ice crystals are avoided. The cooling rate has to be fast in order to avoid the toxicity of the cryoprotectants.

Vitrification of human oocytes then evolved (6). It proved soon more successful than slow freezing (7–11). The feasibility was shown in large oocyte donation programmes. Today, vitrification of oocytes is the most favoured method of fertility preservation. Hence, it is easy to understand that it is also offered to women who want to postpone their childbirths to higher age than is physiologically feasible. It is called egg freezing for non-medical reasons, or social egg freezing.



Egg freezing for non-medical reasons, with the indication to postpone childbirths, is today offered by several private IVF units for women who are willing to buy these treatments. In the USA, big companies, such as Google and Facebook, are offering it for their employees.

### Results from transfer of vitrified thawed eggs

Vitrification of non-fertilized oocytes has been used in units that offer treatment using donated oocytes. The pregnancy rates have been as high as those using fresh oocytes (12–14). A contributing factor to the high pregnancy rates was probably the better quality of endometrium, the cycles in which cryostored oocytes or embryos were used. In light of this, vitrification of oocytes from healthy young women should not be a problem. The reported clinical pregnancy rate per embryo transfer—36.5% when the best embryo was transferred three days after fertilization (15)—is comparable to fresh IVF cycles in most clinics. There are several factors influencing the success rate of vitrification as a method. The laboratory should have extensive experience with the technique before applying it to women. It is important to take into account the known factors that influence the quantity and quality of oocytes. Age is the most important one, but also hereditary and other health factors contribute.

### At which age should eggs be stored?

The optimal age for egg storing is not easy to set. Thinking of biology, it should be done as early as possible. But it should always be the young woman's own voluntary informed choice. Young women are more prone to the most severe complication of oocyte collection, ovarian

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hyperstimulation syndrome (OHSS) caused by the hormones given to mature the eggs. OHSS is potentially life-threatening. It should definitely be a part of counselling. The age of 25 years has been mentioned in literature, but today most women at that age do not yet have any plans for their families. At the age of 36 the situation is much more clear, but the number of potentially collectable oocytes in the ovaries is already then clearly lower even though most frequently very sufficient for a spontaneous pregnancy. The optimal timing was studied by Mesen et al. (16), and at the age of 34 years satisfactory numbers of eggs were still obtained. The average age of the women seeking age-related oocyte cryopreservation in an IVF unit in the UK was 36.7 years, which can be regarded as late (17). The number of oocytes that can be collected decreases with age. It has been calculated that seven eggs have to be stored in order to achieve one pregnancy (18). On the basis of the likelihood to get pregnant after IVF, we know that female fertility significantly decreases after the age of 38 years. This age would obviously be too late a time for oocyte cryostoring. The window appears to be between 25 and 36 years, favouring the earlier rather than the later age. However, few 25-year-old women think of their fertility in the future.

### Awareness of limited fertility period among women is not optimal

There are many social reasons for women postponing their childbearing in the Western world (19). One important reason is the absence of a partner at an appropriate age. Extensive individualized counselling is needed to prevent women and their male partners from 'sleepwalking into infertility' (20–23). Among the reasons, education and career goals have been mentioned. To avoid unnecessary medical procedures, it would be good politically to organize better possibilities for women both to have children and to have working conditions equal to those of males.

Male partners do not always appear to be aware of the fertile period among women. Many men underestimate the impact of advanced female age on fertility and overestimate successful outcome of medically assisted reproduction technology treatment (24,25).

In a study among single women seeking treatment with the use of donated sperm, 91% stated that they would have preferred to have the child together with a partner, and 66% had been in a relationship where they desired to have a child. However, in 40% of these cases the man did not want a child (yet) or did not want more children (had a child/children from previous relationship) (26). In summary, it seems that even more men compared to women are more unaware of risk factors for decreasing fertility (including the risk factor of advanced female age) and often desire family formation at more advanced ages. That supports the finding of Salomon et al. that single motherhood by choice is women's plan

B as many had had a partner who did not (yet) desire a child (26).

### Increased reproductive equity between women and men

Increased equity has been seen as one of the factors favouring oocyte cryopreservation (16,17). It probably does. But at the same time, other means are effective. Making women socially equal would have much fewer side effects for women. Such social and political decisions could be shared parental leaves and equal salaries.

### Conclusions

FP for age-related decrease in female fertility is increasingly needed. Cryostorage of eggs using vitrification is the method of choice today. It is not risk-free. The efficacy is satisfactory, but it is not at all certain that pregnancies are achieved and infants born after every procedure. The age window for social FP is 25–34 years. To prevent all unnecessary complications of medical procedures it would be important to offer counselling to all women regarding decreases in fertility, and even more important to offer equal working conditions for women (shared parental leaves, equal salaries, high-quality day care) who wish to have their children at the physiologically optimal age. These are important tasks for politicians.

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