

# The Future of Elective Oocyte Cryopreservation in Extending Women's Reproductive Potential

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## Mini Review

The rate of first birth to women aged 35-39, as well as age 40-44, continues to increase in the U.S. and many countries [1]. Increasing emphasis on education, later age at marriage, access to effective contraception and opportunity for career advancement are among many reasons for this trend. However, with increasing maternal age, fertility decreases dramatically beginning at 35, due to decreasing oocyte quantity and quality, resulting in increasing chromosomal abnormalities seen in failure to conceive, miscarriage and birth defects [2]. Egg donation, using higher quality eggs from young healthy donors, has historically been the treatment of choice for women wishing to conceive in their fourth and fifth decades of life. The success of oocyte cryopreservation (OC) has led to increased interest in freezing mature oocytes to extend the reproductive capacity in otherwise healthy women wishing to delay childbearing. Planned OC performed at a younger age, prior to decreasing ovarian reserve, allows for having a child using a woman's own genetic material later in life. With improvements in vitrification of mature oocytes, as well as significantly improved fertilization using intracytoplasmic sperm injection (ICSI), the pregnancy rates using cryopreserved oocytes were found to be comparable to those found using fresh oocytes with IVF [3]. More importantly, studies of the health of babies born following the use of oocyte cryopreservation have shown no increase in congenital abnormalities [4,5]. With these reassuring clinical results, OC was no longer considered experimental by the American

Society for Reproductive Medicine (ASRM) in 2012 [6] and has found widespread clinical acceptance.

Because a woman's age, number and quality of oocytes strongly determine the chance of pregnancy, OC cryopreservation is likely to be most successful for younger women [7]. By the age of 38, research suggests that 25-30 oocytes may be required to provide a reasonable chance of pregnancy success [8,9]. The cost of the procedure must be considered, as well as the cost of long-term storage, particularly in young women. In addition, the possibility of achieving pregnancy naturally or with standard fertility treatments, should be taken into consideration when considering planned OC. Due to the fact that at age 20-30, the time of maximal career advancement also corresponds a woman's to optimal fertility, the available option for planned OC has prompted several large corporations to cover the costs associated with the procedure [10], providing additional incentive for career advancement and delayed childbirth.

Cryopreservation of mature oocytes, however, requires controlled ovarian hyperstimulation (COH) using gonadotropin treatment, ultrasound and hormonal testing followed by an outpatient oocyte retrieval procedure, analogous to standard in vitro fertilization (IVF) [11]. Although a single cycle may yield as many as 20-40 healthy mature oocytes for cryopreservation in young women, by the age of 43 only a handful of oocytes may be available. As with standard IVF, multiple egg retrieval cycles may be required, with a significant risk

of miscarriage due to aneuploidy. Alternatives to oocyte donation using known younger relatives or healthy young anonymous egg donors for women in their 4th or 5th decades not fortunate to have availed themselves of the option of planned OC in their 20's therefore has become an area of intense research. In 2016, Hayashi & Saitu reported in Nature, their success in producing stem cells from somatic cells in mice used to obtain mature oocytes that were successfully fertilized and resulted in apparently normal fertile offspring [12]. In-vitro gametogenesis (IVG) has created tremendous interest as well as investment and several venture-capital funded start-ups in the ensuing years have yielded impressive research in the use of stem cells and the use of ovarian organoids resulting in primordial follicle constructs [13]. Such research could provide large numbers of oocytes, without the requirement for planned egg retrieval at a younger age which can be argued to be invasive and expensive for routine use in young women.

Umbilical cord blood banking, which has been commercially available for decades as a means of cryopreserving large numbers of high-quality stem cells tailor-made for an individual. Originally proposed to potentially treat rare cancers later in life through bone marrow transplantation, routine cord blood banking at birth could also provide a readily available pool of high-quality stem cells for IVG later in life. As compared with research in mice, the complexity of human gametogenesis, as well as the regulatory environment surrounding human tissues, and human reproduction, ensure that despite intensive investment in research and impressive progress, clinical acceptance and confirmation of safety is most likely to occur decades into the future. With the proven clinical efficacy and safety of planned OC today as a means of extending the reproductive potential in women who are living longer, often spending more than half of their reproductive lives following natural depletion of their ovarian reserve of healthy eggs, emphasis should be on awareness and information. Analogous to widespread promotion by primary care physicians and gynecologists of effective vaccines against human papilloma virus having a significant effect in decreasing cervical cancer later in life, a similar approach can be applied with reproductive aging. It is not unreasonable to have health care providers inform all young women regarding realistic expectations for the timing of having children as well as their options for delaying starting a family due to educational or career constraints. Several large corporations, including Google and Amazon, have assisted their young female employees by providing insurance coverage to help with the cost involved with planned OC. Although the US military had initially considered such coverage, the rapidly changing political and economic environment the US government has faced in recent years has yet to result in support for this reproductive option for young women. Employer-based healthcare, however, is unique to the US, and other developed countries having universal health care coverage, can allow for better access to health care providers providing the information as well as access to planned OC.

As we have seen with *In-Vitro* Fertilization (IVF), with the birth of Louise Brown in 1978, initially igniting a firestorm of controversy over "test-tube babies", and now is commonly accepted resulting in birth of millions of children today, planned OC is likely in the near term to become commonly accepted as a means of extending women's reproductive potential. The next generation may find it routine to undergo egg freezing in their 20's, have children in their 40's and 50's, and live well into their 90's.

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