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Fertility Preservation and Women's Hopes- The Dilemmas of Social Egg Freezing

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Review

During the last decade, the phenomenon of delayed childbirth and parenting has become more popular among the general population. The effects of aging on reproductive outcomes therefore, have become an area of interest more than ever before [1].

Recent advanced Assisted Reproductive Technologies (ART) enable women as well as men to treat infertility and achieve parenthood against all odds. However, even up-to-date standard fertility treatments or In vitro Fertilization (IVF) "cannot circumvent the biological Clock" [2]. Men produce sperm continuously throughout life from the age of puberty with no significant decrease in fertility. Unfortunately this is not the case when it comes to women. Both the number and quality of oocytes in the ovary decrease and reach to a point whereby women around the age of 50, enter the menopause and are not able to conceive from their own oocytes.

Women's fertility decreases drastically even before the menopausal age. Fertility frequently ends 5-10 years before women reach the age of menopause. The most fertile years of women are between 20-30 years of age. By the time a woman reaches the age of 35, the chances of conceiving is about 20% whereas, at the age of 40, the chances are lower than 5%. [3].

In many countries, the majority of all births are among women over the age of 30. For example, in the Czech Republic birth rate after the age of 30 has changed dramatically from 14% in 1990 to 46% in 2009 [4].

Females who delayed childbearing with or without their willing until their 30 years or 40 years constitute the largest portion of the total infertility population **[5].** The increase in the mean age at first birth among women is related to the spread of the contraceptive pill, which vastly improved women's abilities to plan their pregnancy and postpone childbearing to a later age **[6].** Other factors that lead to late parenthood are rising female employment, expansion of university education, sufficient level of maturity, emotional support and deteriorating economic position of young adults. The most abundant reason for delayed parenting is the lack of a suitable partner **[7]**.

Fertility preservation can be offered due to:

- Medical reasons- before chemotherapy treatment for cancer or other diseases or genetic diseases that may affect ovarian function.
- Non-Medical reasons- in women who chose to defer pregnancy to later in life which is usually referred to as "social oocyte freezing".

There is still a debate around moral and ethical considerations around social freezing of oocytes for the purpose of fertility preservation [12].

Nowadays, Fertility Societies encourage and advice patients with a risk of fertility loss due to cancer or illness to preserve fertility and freeze their oocytes before engaging chemotherapy. However, their recommendations for social freezing are very cautious and not very much elaborated. These organizations send mixed and ambivalent messages to women who are in need to preserve their fertility due to social reasons [3,12]. Moreover, a big debate about this matter is going on in the media and social oocyte freezing is boosting. Many questions and ethical dilemmas about social freezing are brought up more than ever before.

Should the attitude towards fertility preservation be different, if the infertility is caused by illness or age?

Many professionals hold on to the idea that cryopreservation due to social reasons must be kept

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under a tight and a strict watch. They claim that social cryopreservation might contradict with some of the most basic medical ethical codes.

A main ethical issue regarding egg social freezing is the application of medical techniques for non-medical applications, opposed to Hippocrates oath ("Primum non nocere"). The whole process of egg harvesting is very stressful and partially invasive. Like every medical procedure, it has its' own potential risks such as ovarian hyperstimulation syndrome and the surgical risks of oocyte retrieval such as bleeding or infection [13,14]. Another factor that should also be considered regarding the health risks of social egg freezing is that women around the age of 35 would want to have a reasonable amount of oocytes cryopreserved to increase the chances of pregnancy thus, several stimulation cycles will be needed [15].

In medicine, a certain procedure is considered conventional when the benefits of the treatment do not outweigh the risks. Social cryopreservation doesn't meet with the beneficence value. In regular IVF treatments for example, this debate is in favor of the treatment since the mild risks overweigh the successful treatment of infertility. With social fertility preservation, this is not obviously the case and it is far from certain that a woman would eventually use her cryopreserved oocytes reserve for reproduction.

Due to the fact that a woman would not necessarily use there cryopreserved oocytes, many of these oocytes stored in "oocyte banks" will never be used- Is it going to be commercialized? What is going to be done with that reserve? There is no doubt that oocytes cannot be treated as if they were medical waste.

An interesting point that was brought up by Richman [16] is whether and under what conditions infertility should be regarded as a disease. Moreover, he states that fertility preservation aimed to seek medical answers to social problems. As a matter of a fact, modern societies had developed a series of new problems, one of which is the inability of women to build a family during the best age for reproduction. Using fertility preservation as a solution to that problem might deteriorate the problem further and will not resolve this critical social issue [17].

When it comes to fertility, there are no guarantees. Preservation is a relatively new technology and the number of children born as a result of this technique is still limited. Moreover, follow-up data regarding any possible offspring health risks are still being collected and long-term studies are not yet available. The probabilities to conceive from cryopreservation had recently increased significantly [18], however to avoid raising false hopes, women must be informed that the chances of conceiving through natural reproduction at a relative early age are much higher [3,17].

Before going through cryopreservation and before patients develop anticipations, they should be advised to go through cryopreservation prior to the age of 35 in order to increase their success chances. But still, at present, the average age of women deciding to preserve their oocytes is 38 [19].

Another aspect that must be acknowledged is commercial exploitation. Given the very low success rates of cryopreservation for women in their 40s, the potential for commercial exploitation undeniably exists. Women seeking for cryopreservation are often reach their last resort and often are desperate thus, they have a bigger tendency to be used and tricked.

In some people's opinion cryopreservation would also encourage women to further postpone their pregnancies and risk the adverse effects of high risk pregnancies in aged mothers. [20].

More ethical dilemmas arise regarding the harm to children caused by having older or even elderly parents are also mentioned often. According to philosopher [21] there is a great difference between the misfortune of an early death of a young parent, and choosing to set up a situation where there is an increased likelihood of a parent's death while the child is still young [22].

The high cost of cryopreservation has always been a barrier for most women. Cryopreservation generally is not covered by insurance, unless fertility preservation is done due to disease or cancer cases. As a result, it's mostly been a luxury for wealthy women. In addition, doctors recommend patients to buy several rounds of egg freezing in order to increase the number of harvested oocytes and unfortunately many women are lucky enough to afford only one cycle. Patients often waste precious years trying to save up enough money, while their egg quality declines.

A cryopreservation cycle can cost, including expensive fertility drugs anywhere from $10000 to $25000 and additional cycles in order to retrieve enough oocytes may be required. And these are just the costs to retrieve, freeze and store the oocytes, not to thaw them and transfer them to the uterus [23]. Spain and the Czech Republic are popular destinations for this treatment and this has caused medical tourism and cross border reproductive care [24].

ESHRE lately brought up the key question regarding cryopreservation financing: "If society does not pay for elective procedures such as sterilization, why should it pay for fertility preservation? One important difference is that fertility preservation may be seen as a preventative measure with the same aim as assisted reproduction: avoiding unwanted childlessness." [17].

'Freeze and share' arrangement as developed by a British fertility Center (The London Egg Bank) offered a solution for the high cost. Under this arrangement selected women get free ovarian stimulation, harvesting and one year storage in exchange for donating half of their oocytes to program another woman that can get pregnant only with donated eggs. Arrangements of this type undermine the principle of altruistic donation and risks Commercialization. More Ethical concerns arise due to the potential exploitation this program introduces. Fertility centers may lack the clarification about the fact that by relinquishing a patient's oocytes, she automatically become a donor thus, patients may not understand the full meaning of their action.

Despite all arguments against social cryopreservation and the discussions about medical, socio economical and ethical aspects, it seems that "The horses escaped from the stable" and social freezing is on the rise.

Recently, Facebook and Apple made headlines by offering to give female employees $20,000 of cryopreservation benefits [25]. The significance of the Facebook and Apple offer is largely symbolic but it brings social freezing to the center of public discussions.

Public reaction to this news was mixed, especially among women. Some viewed the development positively as a forward-thinking practice that would give greater flexibility and peace of mind to young female employees. Others were skeptical that women would be the true beneficiaries, arguing that it would create implicit pressure to partake in cryopreservation and delay motherhood in order to

demonstrate seriousness and dedication to the workplace.

On the definition side, age-related fertility loss can serve as a very good medical reason for cryopreservation. It is a known fact that increasing age, is associated with low ovarian reserve, oocytes with more genetic abnormalities, increased pregnancy loss and chromosomal abnormalities [26].

Since it is a known fact that diseases occur due to age, it is acceptable to state that oocytes degenerate and deteriorate just like any other organ in the human body. In cases of brain deterioration and dementia patients get treated for an age related problem, just like age-related infertility should be treated.

For those who approve social cryopreservation, fertility preservation can be termed as "preventive medicine" for age-related fertility decline [26]. The European Society of Human Reproduction and Embryology declare (ESHRE) that fertility preservation for natural ovarian aging "cannot so easily be dismissed as a non-health-related preference." [12].

Mertes and Penning G, who investigated ethics and moral aspects of ART and social cryopreservation, raised an interesting analogy for cryopreservation in their review. They compared oocyte freezing to preoperative autologous blood storage for elective surgeries. They claimed that: "the basic structure in both situations is the storage of body material to treat possible future health problems." [27]. According to Mertes H. [28]. "Rather than viewing egg freezing as the alternative to reproducing at a younger age, it should be viewed as the alternative to using a donor egg. From this perspective, egg freezing becomes a form of preventive medicine".

As for the argument of risky medical intervention - Some other procedures like sterilization, termination of an unwanted pregnancy, various esthetic plastic surgeries and donor insemination for single women, might be considered as "medical procedures" to non-medical problems. If those activities are acceptable, it is difficult to declare that fertility preservation should be treated in a different manner. On the same note, the risk factors of oocyte harvesting and ovarian stimulation are much lower than the risks of plastic surgeries and can be prevented easily and effectively.

Ovarian Hyper Stimulation Syndrome (OHSS) is indeed the most common complication of IVF treatments. It is caused by injection of gonadotropins, which are used to hyperstimulate the ovaries to produce multiple follicles and oocytes. Another cause of this condition is ovulation triggering which is performed just 36 hours before the puncture of the ovaries and oocyte retrieval [13]. However, recent research has demonstrated that OHSS can be prevented by using Gonadotropin Releasing Hormone Agonist (GnRHa) instead of Human Chorionic Gonadotropins (hCG) to trigger ovulation before egg retrieval [29]. Unlike the long duration effect of hCG the GnRHa has a very short effect which prevents side effects of OHSS.

Unfortunately, GnRHa cannot be used routinely in IVF because GnRHa treatment to trigger ovulation impairs endometrial receptivity and therefore in IVF treatments with GnRH trigger, fresh embryos cannot be replaced to the uterus and need to be frozen and transferred later in the natural cycle. However, in women who go through oocyte cryopreservation this is not a problem at all since the transfer of fresh embryos in the uterus is not anticipated anyway. Therefore, currently women who undergo stimulation of the ovaries for the purpose of oocyte freezing can be rescued from OHSS.

Other complications such as analgesia due to oocyte retrieval are rare and minimal. Therefore, social cryopreservation possesses relatively much more benefits than disadvantages in terms of health risks [30].

One of the concerns in advising cryopreservation has been the low pregnancy rates achieved with oocyte freezing. However, modern techniques for cryopreservation were recently developed to increase the probability of egg survival after thawing. There are two main methods currently used for cryopreservation labs are slow freezing and vitrification (ultra-rapid freezing).

The vitrification method avoids the formation of ice crystals which are the main cause of oocyte injury during the freezing process [31] therefore this technique of freezing allows better post-thaw survival rates and better live birth rates from frozen embryo transfer cycles [32]. Pregnancy rates following Oocyte cryopreservation have been reported to be similar to the results of standard IVF treatments with fresh embryos and about 5000 babies were born from cryopreservation. [18]. Thus, the chances of pregnancies as a result from a standard IVF/ICSI (Intra Cytoplasmic Sperm Injection) treatment, are similar to the chances of pregnancies from frozen oocytes using IVF/ICSI.

As to the long term health of children born after egg thawing, a recent systematic review collected 22 papers presenting information on neonatal health of children born after freezing of oocytes [33]. The authors conclude that these findings provide reassuring evidence that pregnancies and infants conceived following oocyte vitrification are not associated with increased risk for chromosomal abnormalities, birth defects or developmental deficits. In fact, the age related risk increase for fetal chromosomal abnormalities are halted by cryopreserving the oocytes (if they are frozen in at a young age). Also a review that was done by [34]. comprising 900 verified live born infants resulting from assisted reproduction using cryopreserved oocytes, concluded that compared with naturally conceived infants, there was no difference in the rate of congenital anomalies.

The fact that women usually do not necessarily use all of their frozen oocytes for their own-self use could be a great benefit. These women may donate their remaining oocytes to scientific research or to other women who are in need for oocytes for reproduction. Given the shortage of oocytes for both purposes, this would be an important advantage. In fact, according to the European Society of Human Reproduction and Genetics [17] the greater availability of donor oocytes promises to be an important societal advantage.

I have come to realize that nowadays women may have many good reasons to prefer to postpone childbearing. Unfortunately, a woman's "fertile years" may not align with a woman's preferences.

The argument of increase in maternal age at the time of childbirth due to oocyte cryopreservation and delay in childbirth ignores the fact that many women have similar alternatives and have treatments to conceive by using oocyte donation and have babies at advanced age. In many countries there is a law that dictates the age limit for egg transfer in oocyte donation, that law will obviously also apply for transfer after thawing and fertilization of previously vitrified oocytes. Hence, if women are allowed to have IVF or to undergo oocyte donation treatments in their 50s, then concerns about maternal risks of social cryopreservation are a bit "double standard" and therefore not valid [35].

The Autonomy of a patient is a very strong argument to allow women to decide for themselves whether the fertility intervention is worthwhile in order to preserve the chance of having genetically related children in the future. Women should be able to decide for themselves whether they want to go through the procedure or not. According to ESHRE [17] "A paternalistic attitude from the physician should be rejected" regarding cryopreservation. I do agree that the proper way in medical procedures is to weigh up risks and benefits, but believe it is also important to respect individual's values and involve them in the decision making process.

There have been concerns about the risks for negative psychological effects in children of older parents [17]. However, several studies showed that late parenthood has many advantages such as relational stability, good parent-child interactions, stable financial statues and more time available to become emotionally and psychologically ready to be a parent compared with younger parents [28] reviewed the benefits of being an older parent including benefits for the child in that situation and suggested that instructing society to encourage childbearing at a younger age is not necessarily desirable.

Another aspect of criticizing social cryopreservation is that compared to IVF, cryopreservation and retrieval cost more. Researchers decided to calculate how these costs pay up. In their calculations, they made the following assumptions based on previous studies. They found that 62% of women that froze their oocytes at age 35 and tried to get pregnant at the age of 40 successfully had a baby, with the average total cost of the procedures leading to the birth coming to $39,946. On the other hand, Just 42% of women who tried to get pregnant at age 40 using IVF with newly retrieved eggs conceived, with a total cost of $55,060, on average [36]. It can be concluded that for the long run, cryopreservation might just be a more profitable and practical measure.

In my personal view in the long run, society would definitely benefit from subsidizing oocyte cryopreservation in young women at their thirties. On the long run pregnancies achieved by "youger oocytes" are less likely to have chromosomal anomalies such as trisomy 21 or miscarriages due to other genetic anomalies in aged oocytes.

In 2013 the ethics committee of the ASRM called for programs providing fertility services to “treat all requests for assisted reproduction equally without regard to marital/partner status or sexual orientation.” In addition the ASRM published a research that claims that child development is not harmed in those alternative families [11]. I believe that cryopreservation can fairly compensate for the gender differences and sexual orientation. Besides the fact that all people with no regard to their sexual preferences can enjoy the privilege of building a family, this procedure also promotes sex equality in many aspects. By prolonging the time during which a woman can conceive. It empowers and supports high education, employment and removes the stress of finding an adequate partner. All of these opportunities are increased for women who have more time on their hands.

In summary, in the last decade there has been a demographic shift toward delayed parenting. However, the impact of female age on fertility is dramatic and the implication of delayed childbirth results in drastic decrease in women's chances to conceive.

Recent advances in Assisted Reproductive Technologies (ART) enable oocyte cryopreservation and storage in a bank, with their use later in life to reproduce when fertility is compromised. These advanced techniques raise questions concerning the access to the technology, its permissibility and its use to postpone childbirth. Uncertainty and unintended consequences are key drivers of concern.

While fertility preservation has been strongly encouraged in cancer patients before chemotherapy and other diseases compromising ovarian function, "social egg freezing" still very cautiously advised in healthy women who want to defer family planning.

Social cryopreservation is a medical treatment of a non-medical condition. While individual medical solutions such as ART and elective cryopreservation can promote reproductive autonomy, they entail significant risks and limitations. Socioeconomic, ethical and moral aspects have been under a continuous debate.

Opponents to social cryopreservation argue that it is an invasive procedure, which will encourage women to postpone relationships. They raise the problems of late motherhood and its implications on women and their offspring's health. They also claim that the success of new technologies of cryopreservation yet uncertain and that it may lead to raising false hopes and exploitation. Moreover, they mention the socioeconomical difficulty of attaining such a treatment.

As mentioned above, nowadays we, as a society, experience a revolution in biotechnology and biomedicine. ART had moved so fast in the last few years that even those in the field find it difficult to keep up. To me, applying new technologies are somehow similar to the discovery and use of the "fire". Fire is used in everyday life and enables the survival of the human kind. It is used for warming up in freezing days, for cooking food, for boosting up the industrial world and for many other essential actions. Nevertheless, fire should be used cautiously, as it can also burns or even worse-kill in minutes.

If we had stopped medical progress and banned the use of IVF in 1978 just because innovations may be scary, the 5 million IVF babies that were born by ART, would have never been born. Just like IVF, oocyte freezing is another significant medical advance with dramatic implications on society and women's freedom.

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