# Egg Freezing and the Impact of the COVID-19 Pandemic

## Criopreservação de Ovócitos e o Impacto da Pandemia COVID-19

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## Abstract

Egg freezing has evolved over the last decades, becoming an accepted and recognized technique for fertility preservation. This technique has various medical and non-medical indications and it is becoming an important step in overcoming age-related declines in fertility. Nonetheless, since it remains inadequately understood by the general public and medical professionals, raising its awareness is of vital importance. There are numerous factors that influence the technique's success, particularly the number of matured eggs retrieved and the woman's age, which affects the quantity and quality of oocytes. Women were prompted to more seriously contemplate social egg freezing throughout the COVID-19 pandemic, given that social isolation complicated their search for an ideal male partner and allowed for more time to consider and research this topic.

## Resumo

A criopreservação de ovócitos evoluiu ao longo das últimas décadas, tornando-se numa técnica aceite e reconhecida de preservação de fertilidade. Esta técnica tem várias indicações médicas e não médicas e, além disso, tomou um papel importante no combate ao declínio da fertilidade associado à idade. No entanto, a sensibilização da população, no geral, e dos profissionais de saúde é fulcral, devido à falta de conhecimento inerente ao tema. Existem vários fatores que influenciam o sucesso da técnica, particularmente o número de ovócitos maduros colhidos e a idade da mulher, que afeta a quantidade e qualidade dos ovócitos. As mulheres acabaram por ponderar mais seriamente o congelamento social de óvulos durante a pandemia de COVID-19, já que o isolamento social complicou a sua busca por um parceiro masculino ideal e permitiu mais tempo para considerar e pesquisar este tópico.

**Keywords:** Cryopreservation; Fertility Preservation; Reproductive Techniques, Assisted; Sperm Injections, Intracytoplasmic

**Palavras-chave:** Criopreservação; Preservação de Fertilidade; Técnicas de Reprodução Assistida; Injeção Intracitoplasmática de Espermatozoides

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# Introduction

Cryopreservation refers to the process of cooling cells and tissues at subzero temperatures such that their viability is preserved for future use.[1] Although the application of this technique to human embryos and sperm has been well-established for many years, only recently has the cryopreservation of oocytes become widespread. This is due to the inherent cellular characteristics of the oocytes, which are more susceptible to the physical and chemical stress of freezing. Oocyte cryopreservation, through the method of vitrification, has become the most effective method for women wishing to preserve their fertility. This technique, characteristically applied towards fertility preservation due to medical reasons, can also be used in the context of Medically Assisted Reproduction (MAR) techniques and for social egg freezing.[2]

## Indications for treatment

The indications for undergoing oocyte cryopreservation can be either medical or non-medical. Initially, the only recognized indications were oncologic, applying to women submitted to either chemotherapy or radiotherapy, both of which have gonadotoxic side-effects.[3,4]

Other medical indications for oocyte cryopreservation include autoimmune diseases, endometriosis, and hematological diseases that require hematopoietic stem cell transplant, which incur a high risk of developing ovarian failure. Certain genetic diseases are other potential medical indications. In some of these women, oocyte quality may be reduced even prior to undergoing treatment, underscoring the importance of considering fertility preservation before the start of the treatment, with the aim of maximizing future reproductive potential.

In the context of MAR, oocyte cryopreservation can be used in cases of failure in the collection of the sperm sample, unavailability of the male partner on the day of the ovarian puncture, in women with low ovarian reserve, in oocyte donation programmes, and in planned female-to-male transitions.[3,4]

Although it is well established that female fertility decreases throughout life and that delaying pregnancy can mean its compromise, the general public and many medical professionals are unfortunately still unfamiliar with these facts. Currently, women get pregnant at ever-later ages for several reasons, be they professional or personal, such as choice of partner and financial aspects.[4,5] Consequently, women are beginning to seek preservation of their fertility so that they may effectively "delay" their pregnancy.

We thus face a relatively recent concept, which is the elective cryopreservation of oocytes, also known as social egg freezing. The rationale for this approach is based on the fact that the ovarian reserve begins to decrease from 30 years of age, with a more significant decrease from age 35 onwards. Furthermore, as it allows for the use of a woman's own oocytes, it may permit women to have biological offspring at age ranges where natural conception is less likely and IVF success rates lower.[6]

It is thus pertinent to discuss the main advantages and disadvantages of this technique. Regarding its advantages, by allowing women to preserve their fertility, their reproductive autonomy is enhanced. The treatments are also very safe, with the rare complications of ovarian hyperstimulation syndrome, bleeding, infection or anesthetic-related complications during oocyte pickup.[6] It is important to note that undergoing this procedure does not interfere with a woman's future fertility. With regards to legal and ethical aspects, this is the indicated option in cases of fertility preservation.[5]

With respect to the disadvantages, this technique has the potential to give women false security regarding their ability to have children in their future.[2] Likewise, postponing pregnancy to more advanced ages carries with it inherent risks. Regarding costs, in the Lusíadas Hospital Lisbon, the price for an oocyte cryopreservation cycle is 1260€, with an additional 5-year storage cost of 600€. Although this represents an accessible price for many women and is subsidized by some employers (such as Google and Facebook), it is not currently reimbursed by health insurances. Furthermore, if a woman ends up not making use of her cryopreserved oocytes, this invasive procedure and associated costs can prove to have been unnecessary.[4]

## Success of cryopreservation

There are a variety of factors that influence the success of oocyte cryopreservation, of which the woman's age and number of mature oocytes are the most important, in this order. In order to maximize the quality and quantity of oocytes, the cryopreservation should be done as soon as possible. Notwithstanding, the ideal age range in terms of cost-benefit is between 30 and 35 years of age, because if the procedure is done earlier, there is less probability of oocytes being used in the future.[4] Even so, the technique should be recommended in younger women with diminished ovarian reserve, or those at risk of premature ovarian failure. Cryopreservation at more advanced ages can require a more elevated number of cycles, with far lower success rates, which partakes larger physical, mental, and financial tolls. The number of frozen mature oocytes is, as stated, another crucial factor in the success of this procedure. In theory, in ages under 38, the ideal number of mature oocytes is 15-20, whereas in ages over 38 the number is 25-30.[2,4] Clinical practice tells us that, in reality, it is very hard to achieve these numbers in all women and usually requires many oocyte pickups.

A very important point, already commented, is that there is a widespread lack of awareness of the impact of age on a woman's fertility. It is thus imperative to educate all sexes and ages so that women try pregnancies at younger ages and, if this does not happen, that they seek this technique as soon as possible. If this is done, when comparing the utilization of fresh oocytes in 40 year-old women to those with 30 years, the success rates per transfer increase from 6.6% to over 40%.[5]

## Techniques

Oocytes are inherently more susceptible to the processes of freezing and thawing due to their larger size and water content. Oocytes are frozen during metaphase II, since there is already a complete maturation of the nucleus and cytoplasm and the chromosomes are condensed and organized in the center of the cell. These oocytes are extremely sensitive to freezing and are much more susceptible to cryogenic lesions than spermatozoids and embryos. This is a consequence of their cellular characteristics, as they have a greater dimension and volume of water.[1]

The process of cooling cells involves changes in the cell surface--to-volume ratio, as it creates extreme fluctuations in the intracellular water volume. It brings cells to negative degrees Celsius of temperature, which stops all cellular molecular activity and physiological functions, mandating the addition and removal of cryoprotectants that themselves alter normal cell physiology. Biological damage, that may not be microscopically visible at first and may only cause impairment later in the process (i.e. in fertilization and initial embryonic development) include precocious hardening of the zona pellucida, in vitro aging, spontaneous activation of the oocytes, and DNA fragmentation. It is worth noting that only the first two aspects are proven to occur and to have clear and direct consequences. All frozen oocytes must be fertilized with Intracytoplasmic sperm injection (ICSI).[1]

Specific cooling protocols, which make use of cryoprotectants, have been developed to circumvent these problems associated with freezing. The objective of these substances is to stabilize the cell and its intracellular proteins, impeding the formation of ice crystals and creating osmotic gradients to induce dehydration.[1] The success of the most recent technique of vitrification, which involves ultra-fast freezing of cells in liquid nitrogen, has been responsible for making oocyte cryopreservation as widespread as it is today. In contrast to the previous method of slow cooling, vitrification shows a much lesser impact on the oocyte's viability.[7,8]

## COVID-19 pandemic

The COVID-19 pandemic, by sewing uncertainty regarding its spread and effects on pregnancy, cast serious doubts on all MAR centers on how to manage women seeking treatment. In March of 2020, strict precautions were put in place that were only gradually subsided in the later months.

The impact of the first lockdown on Portuguese MAR centers was thus extensive, causing a cancellation or delay of 2900 cycles and a reduction of 48% and 33% in Public and Private institutions, respectively.[9,10] The large drops in activity, however, were not solely due to the Medical Societies' recommendations for delaying certain treatments. Other contributory causes included multiple delays in new diagnoses of infertility, referrals to MAR centers, reproductive surgeries and in multidisciplinary consultations.

Portugal, in line with the majority of European countries, maintained access to urgent fertility treatments, including cryopreservation for medical reasons.[11]

The delayal or cessation of treatments still imparts a significant impact to the psychosocial health of women undergoing MAR treatments. Fear of the virus and additional travel to medical centers caused many oncologic patients to give up on MAR, and thus the possibility of future pregnancies.[12] These concerns are compounded by reductions in the financial capacity of some women and the increasing costs in access to MAR, such as hospital personal protective equipment and the need for COVID-19 testing. Ultimately, the delaying of MAR treatments has resulted in still-present disastrous complications for many fertility patients, in particular to those with diminished ovarian reserves.

With regards to social egg freezing there is, however, evidence of increased interest in, and in some cases the fulfillment of, this technique.[13] This can be explained by the fact that social isolation hampered the possibility for many women to seek a suitable partner, besides providing a greater opportunity to reflect on, and investigate, different options for family planning. Furthermore, employers have increasingly included social egg freezing in their benefit packages of job offers, as a means of attracting women workers.

# Conclusion

Oocyte vitrification in order to preserve fertility is currently a well-founded technique, with proven efficacy and security for many different indications, be they medical, non-medical, or as a help in MAR techniques. One should be aware of the fact that, independently of the indication for fertility preservation, cryopreservation is by no means a guarantee of pregnancy, instead serving as a means to increase the probability of having a future biological child. Unfortunately, to this day, there is still a large lack of awareness of the existence and nuances of this

technique, among women and healthcare professionals alike. Knowledge on this topic by medical practitioners proves essential so that they can properly inform and advise patients they follow on a regular basis, in addition to understanding when to refer their eligible patients in a timely manner.

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## Responsabilidades Éticas

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