FERTILITY PRESERVATION

A guide for people facing an illness or life events that may affect their fertility

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Acknowledgements

Graphics derived from:
[page 6] *Supplement to the 'Egg freezing in fertility treatment' report*, Human Fertilisation & Embryology Authority, London, 2018, https://www.hfea.gov.uk/media/2658/egg-freezing-in-fertility-treatment-supplement.pdf, consulted 11 March 2021;
[page 7] Kuliev et al. Meiosis errors in over 20,000 oocytes studied in the practice of preimplantation aneuploidy testing, *J Reprod Biomed Online*. 2011 Jan; 22 (1): 2-8.

This guide has been drawn up by the Council of Europe European Committee on Organ Transplantation (CD-P-TO). For more information, please visit https://go.edqm.eu/transplantation.

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INTRODUCTION

Fertility preservation is the process of saving or protecting a person's oocytes (also known as 'eggs'), sperm, reproductive (ovarian/testicular) tissue and/or embryo(s) so they can use them to try to have biological children later in life. In most cases, fertility preservation is done through a process known as cryopreservation, by which viable oocytes, sperm, tissues or embryos are frozen and stored.

Preserving your fertility involves freezing your oocytes, sperm, embryos or reproductive tissue so that you can hopefully have a biological family in the future. These procedures can be considered for persons who may, for different reasons, undergo a decline in their capacity to procreate naturally later in life.

Some of the current indications include:

- ✓ People who are about to undergo chemotherapy and/or radiation therapy to treat cancer.
- ✓ People with other severe non-malignant diseases requiring medical treatments that may affect their future fertility.
- ✓ People with genetic diseases that will affect their future fertility.
- ✓ Women who need to undergo surgery that will inevitably affect their ovarian tissue.
- ✓ Transgender or non-binary people who are about to start hormone therapy or are planning to have genital reconstructive surgery.
- ✓ Women who want to delay having children and wish to lessen the negative effects of ageing on the number and quality of their oocytes.
- ✓ Men whose jobs might compromise their fertility, or who decide to have a vasectomy for contraceptive purposes.

The assessment, counselling and approach for fertility preservation will depend on the type of life event or the severity of the disease, the patient's age and the treatment to be received. Any person considering fertility preservation should be referred to a fertility clinic/expert who can tell them more about their risk of infertility, their fertility preservation options and the possible future use of their cryopreserved oocytes/sperm or tissues.

The storage of cells and tissues and their subsequent use to restore fertility may, in some cases, involve medical procedures that are currently regarded as experimental. Moreover, the ethical implications of some of these techniques are viewed differently around the world. It is therefore possible that some of the procedures described will not be offered in all countries.

This booklet describes situations in which fertility preservation may be considered, the cryopreservation techniques available and the possible uses of stored cells, tissues and embryos. It is intended to provide readers with clear, accurate and balanced information that will guide them through the different options so they can ask the healthcare professionals treating them the right questions and make informed decisions according to their needs and values.

This guide has been prepared by the Council of Europe **European Committee on Organ Transplantation (CD-P-TO)**, composed of internationally recognised experts, in collaboration with the **European Society of Human Reproduction and Embryology (ESHRE)**, to provide clear, accurate and balanced information about fertility preservation.

FERTILITY PRESERVATION: OOCYTES AND OVARIAN TISSUE

Unlike sperm, which are produced in the testicles from puberty onwards and throughout life, all oocytes are produced before birth during foetal development and stored in the ovaries in small pockets called follicles. This so-called 'ovarian reserve' of oocytes can be affected by a number of factors. For example, chemotherapy and radiotherapy treatment for cancer and other severe non-malignant diseases, e.g. auto-immune conditions/diseases such as lupus or blood disorders such as aplastic anaemia or thalassaemia, may destroy some or even all of the oocyte-containing follicles in the ovaries, causing loss of fertility. With more and more people of reproductive age surviving cancer or other severe diseases, an increasing number of people will be affected by these side-effects.

Surgical procedures can also have an impact on fertility. For example, during surgery for severe endometriosis or to remove benign ovarian cysts, it is sometimes necessary to remove healthy surrounding ovarian tissue together with the viable follicles and oocytes it contains.

Some genetic diseases, such as Turner syndrome or galactosaemia, can also cause early loss of ovarian function before the body even reaches adulthood: fertility preservation may also be appropriate in these cases.

Furthermore, transgender or intersex persons planning to start hormonal treat-

If you are about to start chemotherapy, possible ways to keep your fertility include:

- freezing oocytes
- freezing embryos
- freezing ovarian tissue.

Unfortunately there can be problems with these methods and they are not suitable for everyone.

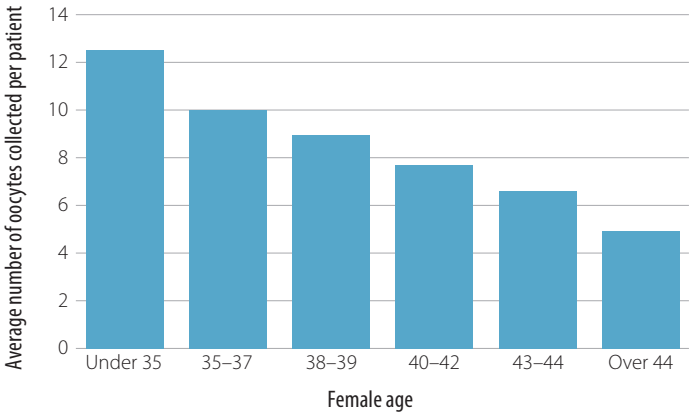
ment or to undergo surgery involving their ovaries may wish to consider their fertility preservation options before starting treatment.

In all of these cases, the risks of undergoing fertility preservation, including performing invasive procedures, and any possible delays to receiving curative treatment for the disease, should be explained in full and weighed against the benefits of having cells and/or tissues stored for future use.

Age-related fertility preservation

As the body ages the number of oocytes in the ovaries declines and the 'quality' of the remaining oocytes (i.e. their ability to be fertilised, to develop into embryos and into a healthy pregnancy) decreases.

Age-related decline in the number of oocytes

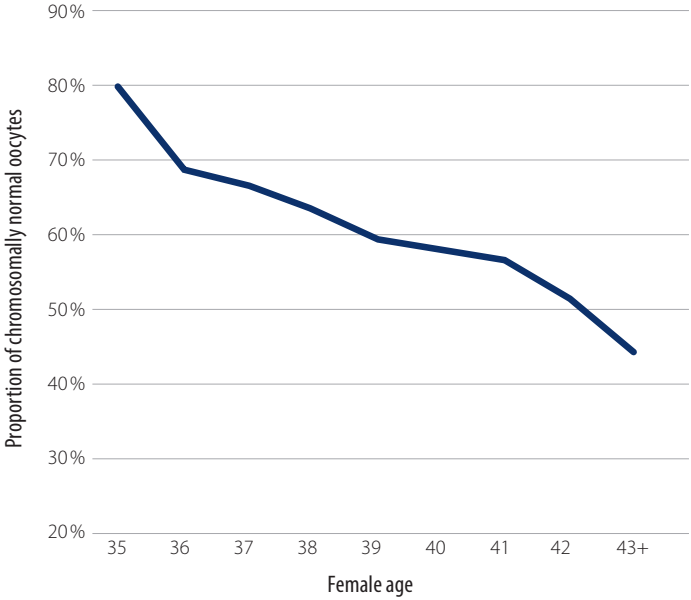


As women get older, both of these factors will negatively affect the possibility of giving birth to a healthy child. Therefore, women who are not ready for a family and wish to postpone motherhood (because they haven't

met the right partner, they don't feel financially or emotionally ready, or have other life plans they want to pursue) may consider fertility preservation as a means of protecting some of their oocytes against the effects of ageing. This is sometimes referred to as social or age-related fertility preservation.

However, due to the declining oocyte quality, it is important to bear in mind that the success rate depends very much on the age of the woman at the time the oocytes are cryopreserved and there is no guarantee that she will be able to give birth to a biologically related child in the future.

Age-related decline in the quality of oocytes



Oocyte preservation

In order to increase the number of mature oocytes to be collected at the same time, pa-

Different options for female fertility preservation include:

- freezing of unfertilised oocytes
- freezing of fertilised oocytes (embryos)
- freezing of surgically removed ovarian tissue.

tients are given hormones to stimulate their ovaries. This procedure is similar to ovarian stimulation for *in vitro* fertilisation (IVF).

Hormone injections are given to boost the number of oocytes produced by the ovaries and also for inhibition of the spontaneous ovulation. This takes around 8–12 days and is monitored by transvaginal ultrasound examinations and blood samples, which help the physician determine when the oocytes are ready for retrieval. A number of visits to the clinic will be necessary during this time.

About 36 hours before the actual oocyte retrieval, a hormone injection is administered to help the oocytes mature. The mature oocytes are then collected from the ovaries using a vaginal ultrasound probe. A needle connected to a suction device is guided through the vaginal wall into each ovary in turn, and the oocytes are aspirated one at a time. This procedure, which takes around half an hour, is usually performed under local anaesthesia with or without sedation, or sometimes under general anaesthesia.

The fertility drugs given to stimulate oocyte production may cause some mild side-effects that include hot flushes, feeling irritable or down, headaches and restlessness. The most important possible medical complication of ovarian stimulation is ovarian hyperstimulation syndrome (OHSS), a condition in which the ovaries show an excessive response to the hormonal treatment and become swollen and painful. Up to 30 % of women undergoing ovarian stimulation experience mild hyperstimulation with symptoms such as a swollen stomach and stomach

pains, which can be managed with standard pain relief. In extreme cases, nausea, vomiting, breathlessness, fainting and reduced urine production may be experienced. However, with today's modified stimulation regimes, the serious forms of ovarian hyperstimulation are extremely rare. Nevertheless, none of these symptoms is to be taken lightly and it is important for anyone experiencing a reaction to their fertility drugs to contact their clinic immediately.

Aspiration of oocytes is generally very safe; most patients don't experience any problems beyond the discomfort of the procedure itself, although there may be a slight risk of bleeding or infection. Some patients may also experience mild discomfort after the procedure but this usually disappears within a few hours.

Once the mature oocytes have been collected, they are cryopreserved in the laboratory via a process called vitrification, and stored at a very low temperature in liquid nitrogen. They can then be kept for many years (14 years is the longest officially reported time at present).

Ovarian tissue cryopreservation

In the case of a girl who has not entered puberty at the time of treatment (chemotherapy, for example), a loss of all follicles will mean that she will not enter puberty without medication and that she will not be able to become pregnant with her own oocytes later in life. In these prepubertal patients, the hormonal stimulation treatment, oocyte collection and freezing procedures described above

are not recommended. However, even before puberty, the ovaries contain large numbers of immature oocytes in their follicles and it is possible to freeze ovarian tissue to preserve fertility at any age. This option – called ovarian tissue cryopreservation – can also be offered to adults, for instance when ovarian stimulation and oocyte cryopreservation is contraindicated or not feasible due to time constraints.

Removal of small pieces of the ovary, or of a whole ovary, is done by 'keyhole' surgery under general anaesthesia, and usually takes less than an hour to perform. For children, the procedure will be carried out by a paediatric surgeon. Most patients will be able to go home in the evening of the same day.

As with any other surgical procedure, complications may occur. There can be bleeding, but this is often minor and is detected during surgery. Infections can occur days to weeks after the surgery, but this is rare. A serious complication to the surgery is accidental damage to the bowel which may require further surgery to repair it. All these occurrences are rare, and in most cases the surgery is without complications.

After the tissue has been prepared by dissecting it into smaller pieces, it is stored in liquid nitrogen and can remain frozen for many years.

Future use of cryopreserved oocytes and ovarian tissues

Whatever their age, patients undergoing fertility preservation should always be in-

formed of the possible uses of their oocytes or ovarian tissue in the future. It is important to understand that there is no guarantee that the stored oocytes, embryos or ovarian tissue will enable the patient to become a parent in the future. Other family building options should therefore be discussed during fertility preservation counselling.

Female-to-male transgender patients wishing to consider fertility preservation should be informed that possible options for the use of their oocytes in the future may vary in different countries according to national legislation.

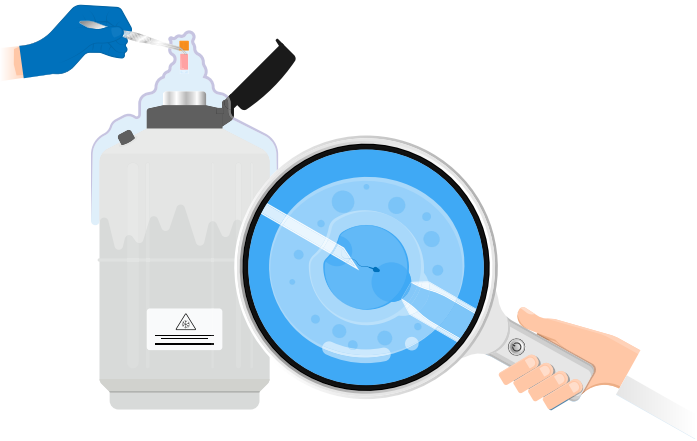
Current data indicate that about a third of patients who have their frozen ovarian tissue re-implanted give birth to a (healthy) child.

The chance of a successful pregnancy in the future will depend on many things. Cryopreservation techniques for oocytes have improved much during the last years, and in general, patients with cryopreserved oocytes have the same chances for the birth of a (healthy) child as other women going through IVF treatment. However, in the case of adult women, age at the time of oocyte collection is the most important factor for success (see graphics, pages 6 and 7). In addition, the oocytes may have been affected already before collection, by the disease or by medical treatment.

Many patients with ovaries will remain fertile after cancer treatment. Even if the menstrual periods stop during treatment, they often come back later. In this case, the frozen oocytes or ovarian tissue may not be needed. However, sometimes fertility is lost and the patient may want to use their frozen oocytes or ovarian tissue to become pregnant. If their treating doctor thinks it is

safe for them to become pregnant they may be referred to the fertility clinic that stored the oocytes/ovarian tissue. The doctor will assess whether it is safe to attempt a pregnancy, taking into account any potential delayed effects of the cancer treatment, the age of the patient and time since the end of treatment. The doctor may advise delaying a pregnancy, or may recommend close monitoring during pregnancy to ensure the health of both parent and baby.

If the patient's oocytes have been cryopreserved, they must first be fertilised using sperm from the partner or from a sperm donor. Thereafter, an embryo replacement cycle must be planned. This may involve treatment with hormones to prepare the lining of the womb (the endometrium) to accept the embryo for implantation, as well as blood tests and ultrasound screening.

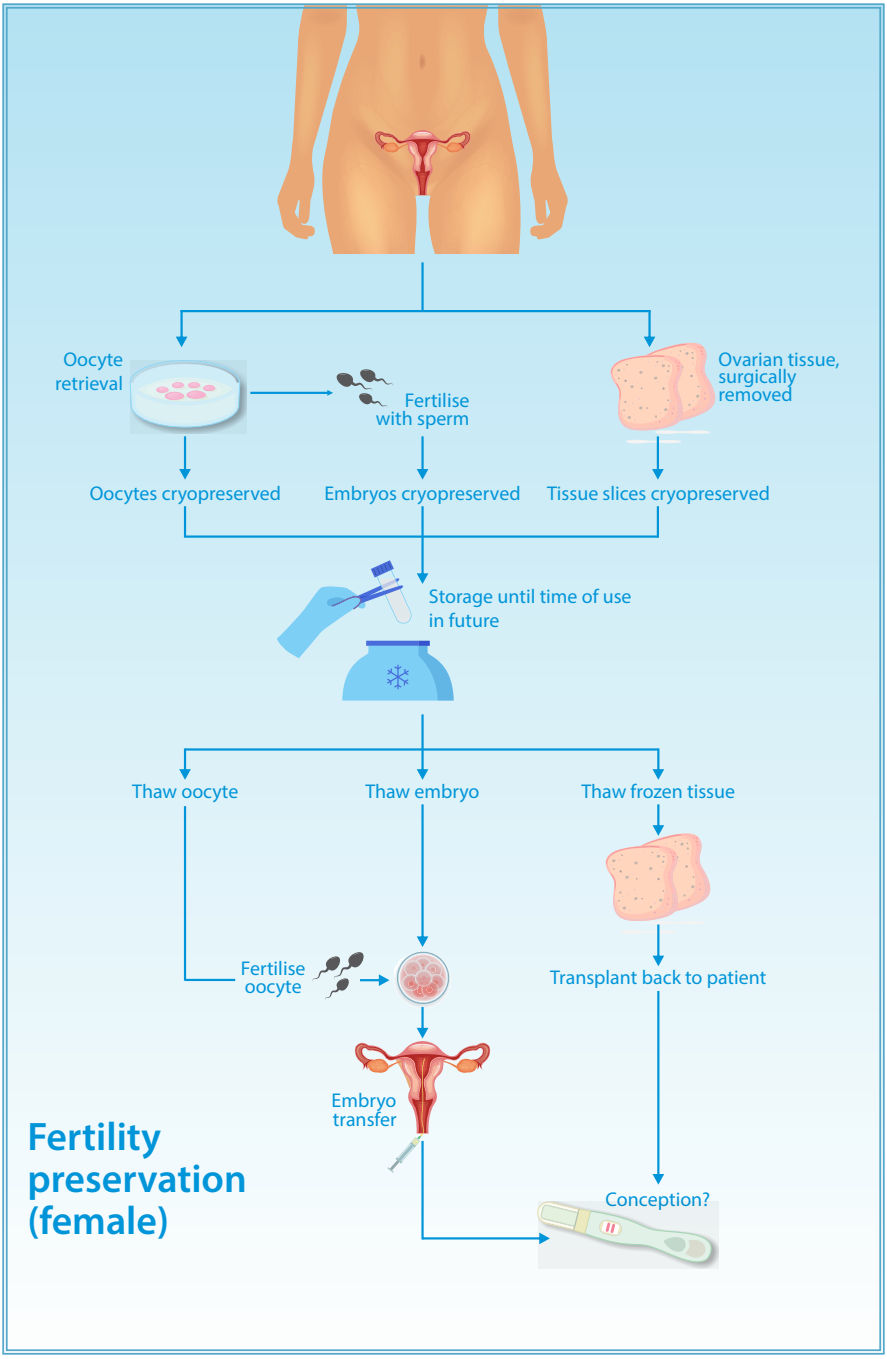


The process is slightly different when ovarian tissue rather than oocytes is preserved. While ovarian tissue may contain a large number of ovarian follicles, the

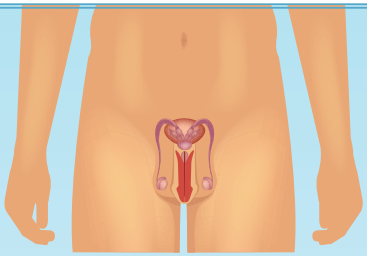
oocytes within the tissue are very immature compared to those collected after ovarian stimulation. For the oocytes to mature (a process that takes several months), the tissue has to be replaced inside the body. This requires another keyhole operation. Typically, a third or up to half of the collected pieces of ovarian tissue will be thawed and replaced, either into the remaining ovary or close to the site of the removed ovary. In most cases, after a period of a few months, the tissue will start working and will produce oestrogen, triggering ovulation and menstruation. Some women will be able to become pregnant without medical assistance following this procedure whereas others may need fertility treatment such as IVF.

It is important to recognise that ovarian tissue replacement is still regarded as innovative: relatively few children have been born this way and long-term safety data are not yet available. However, ovarian tissue cryopreservation is available in most European countries.

It is also important to consider the possibility that cryopreserved ovarian tissue may contain cells from the original cancer and that these cells may become active again after the tissue replacement. For many cancers, this risk is low, but for some, particularly leukaemia, the risk may be considerable. The ovarian tissue should therefore be tested before being re-implanted. Patients should be informed of the possible risks of tissue replacement and specifically that it is impossible to guarantee that the implanted tissue will be cancer-free.


Oocyte retrieval
Fertilise with sperm
Ovarian tissue, surgically removed
Oocytes cryopreserved
Embryos cryopreserved
Tissue slices cryopreserved
Storage until time of use in future
Thaw oocyte
Thaw embryo
Thaw frozen tissue
Fertilise oocyte
Transplant back to patient
Embryo transfer
Conception?
Fertility preservation (female)

Fertility preservation (male)



Sperm sample by ejaculation

Aspiration of sperm from testis

Tissue biopsy from testis

Sperm cryopreserved

Tissue samples cryopreserved

Storage until time of use in future

Thaw sperm

Thaw testicular biopsy

Fertilise oocyte

Sperm extraction from tissue

Embryo transfer

In the future? Transplant tissue back to patient?

Intrauterine insemination

Conception?

FERTILITY PRESERVATION: SPERM AND TESTICULAR TISSUE

Production of sperm in the testicles starts at about 13 years of age and generally continues throughout life. However, chemotherapy, radiotherapy, hormonal treatments and certain surgical procedures can damage the production of sperm. The extent of damage to the testicles depends on the type of treatment and the individual. About 60 % of male cancer patients will face (in)fertility problems after the end of treatment. While the loss of fertility can be temporary and they may recover their ability to produce sperm, it can also be permanent. Permanent loss is often difficult to predict in advance,

Some medical treatments can:

- reduce the number of sperm you produce
- affect the sperm's ability to fertilise an oocyte
- affect the production of the reproductive hormones
- affect the nerves in the genital area, making it difficult to get or maintain an erection.

Talk to your doctor about your risk of infertility. They can tell you more about the possibility of storing sperm.

and depends on the type of illness and the treatment received for it. All patients at risk of fertility loss (or their parents in the case of minors) should be informed about available fertility preservation options.

Furthermore, transgender or intersex persons planning to start hormonal treatment or to undergo surgery involving their testicles may wish to consider their fertility preservation options before starting treatment.

Preservation of sperm

Sperm samples can be collected from adults, from postpubertal youngsters and even from peripubertal patients if they are able (and willing) to produce a sample by masturbation. The circumstances under which the sample is collected and delivered to the laboratory can influence its viability and patients will be provided with clear instructions regarding collection (hygiene, sexual abstinence, timing, etc.). If the sample can be collected in a dedicated room adjacent to the laboratory, the risk of delays during transportation and cooling of the sample is minimised.

If for any reason the patient has difficulty providing a sperm sample by masturbation (e.g. spinal injury) this should be discussed with the treatment team at an early stage so that alternatives can be considered. These may include the use of penile vibratory stimulation or surgical recovery of sperm directly from the testicle.

Following collection, sperm samples will be processed and prepared for cryopreservation in liquid nitrogen.

Testicular tissue cryopreservation

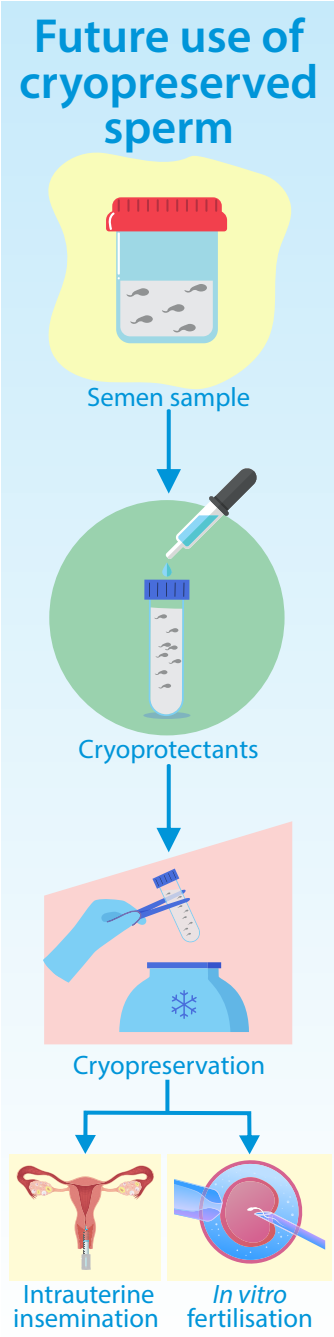
For patients who cannot produce an ejaculate, or who do not have sperm in their ejaculate, a piece of testicular tissue can be surgically removed to be frozen and stored. As with any surgical procedure, there is a small risk of pain, bleeding or damage to the testicle.

As the testicles only start to produce sperm at around the age of 13, this is also an option for prepubertal patients. However, while it is considered safe and effective for adults, its use for prepubertal patients is currently considered experimental and its suitability should be discussed very carefully with the treatment team on a case-by-case basis.

Future use of cryopreserved sperm and testicular tissues

Patients undergoing fertility preservation should always be informed of the possible uses of their sperm or testicular tissue in the future. It is important for them to realise that there is no guarantee that the stored sperm or testicular tissue will enable them to become a parent in the future. The sperm sample may have been affected already before collection, by the disease or by medical treatment.

Some patients will regain their ability to produce sperm after their treatment. If that is the case, they will usually do so within



5 years following the end of their last treatment. They should therefore be offered regular semen analysis tests once their treatment has ended.

Male-to-female transgender patients wishing to consider fertility preservation should be informed that possible options for the use of their sperm in the future may vary in different countries according to national legislation.

Sperm can be frozen for many years (more than 25 years has been reported), with good survival rates and capacity for fertilisation. While the freezing and thawing process may reduce the overall quality of the sperm sample by decreasing the percentage of live and motile sperm, it is highly unlikely that all sperm are lost, and in most cases there will be at least some sperm that will survive and can be used for fertilisation. Importantly, those sperm that survive the process will have the same fertilising capacity after thawing as fresh sperm.

Even if only very few sperm can be recovered from a thawed sample, it may be possible to use them in a fertilisation procedure called intracytoplasmic sperm injection (ICSI), in which a single sperm is injected directly into an oocyte. This means that the patient's partner will have to go through an IVF procedure, with ovarian stimulation and collection of oocytes. The success rate with ICSI is the same as with IVF for someone with a normal sperm count.

There is currently no consensus on how to thaw and then use prepubertal testicular tissue to produce sperm. Many research

programmes are trying to figure out the best way to do this, but it is likely to be several years before a technique is ready for routine use. Young patients who have their testicular tissue stored should contact their treatment team for information on how the science is progressing and what options might be available for them in the future.

CONSENT FOR TREATMENT

Free and informed consent for the collection and preservation of reproductive cells and tissues must always be obtained. However, individual countries may have specific laws about how this is obtained and how frequently it needs to be reviewed or renewed.

Storage and use of sperm and embryos
Consent form

First name(s)

Surname

1. Use

a. I consent to the use of my sperm for the following purposes:

- in treating a named partner ☐ yes ☐ no

  full name of partner

- in treating others ☐ yes ☐ no
- in any research project ☐ yes ☐ no

By signing this form you agree that you have been fully informed about the procedures and have been offered counselling. You may change the terms of your consent, or withdraw it entirely, at any time except in relation to sperm or embryos which have already been used.

Specific consideration should be given to children, and in this case informed consent may need to be obtained from parents or legal guardians.

The information provided to patients should include details on whether a procedure is considered experimental.

The consent form or related information leaflet should provide details on how long oocytes/sperm or reproductive tissue can be stored and on any potential treatment-related risks.

It is important to note that while cryopreserved oocytes/sperm belong to the indi-

Consent is an essential part of your treatment and, together with your clinic, you should make sure you fully understand all the issues before giving your consent. You should be given full information about your treatment before you consent, and your decisions will have important implications for how your gametes, embryos or tissues can be used in the future.

vidual who produced them, in the case of a couple storing embryos these belong to both members of the couple. This means that, if the couple separates, for example, one partner may not be able to use the embryos without the consent of the other. In some countries, this may also hold true in the case of death of one member of the couple.

In addition, in many countries, post-mortem use of preserved tissues or oocytes/sperm by the deceased's family or partners is either not allowed or their use is subject to the deceased person having provided specific consent for this circumstance prior to death.

TAKE-HOME MESSAGES

People with certain diseases, disorders, and life events that affect fertility may benefit from fertility preservation. This option should always be proposed to prepubertal patients and to adults of reproductive age who are at risk of becoming infertile due to malignant disease or other conditions. Some people may also consider oocyte/sperm cryopreservation for non-medical reasons, to postpone parenthood for example.

The assessment, consultation and method of fertility preservation will depend on the specific situation of each patient, their age and the treatment to be used.

Anyone considering fertility preservation should be referred to a fertility clinic/expert, who will provide them with more information about their risk of infertility, their fertility preservation options and the possible future use of their cryopreserved oocytes/sperm or tissues.

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