

"I was 26 when I was diagnosed with Hodgkin lymphoma in 2015. I knew before starting cancer treatment that it is possible to preserve fertility. But having been knocked flat by months of illness and still dazed by the diagnosis, I didn't think to raise it. I was certain the oncologist would take care of it. I remember thinking: 'he knows what he's doing'."

Perhaps he didn't. Because Elena's story (not her real name) is not a good example of what should be done in such circumstances. "In the end, the oncologist did warn me that the treatment I had to undergo could compromise my fertility, but he told me just a day before I started chemotherapy. There was no time to cryopreserve oocytes [immature eggs] or ovarian tissue – the techniques considered most effective to preserve fertility in cases like mine."

Today Elena feels good. She defeated her disease, and during chemotherapy she was treated with a drug that put her ovaries into temporary hibernation, which helps protect them from the toxic effects of anticancer therapy. She hopes that this will still give her a chance to have a child sometime in the future. In the meantime, she is helping other women who find themselves in a situation similar to the one she experienced a few years ago. She is volunteering with [Gemme Dormienti](#) (Sleeping Buds), an association dedicated to informing health professionals and the public about fertility preservation for cancer patients. "Unfortunately," she tells us, "there are still many women with cancer who are not informed about this, and do not get the guidance they need to pursue fertility preservation after they are diagnosed with cancer."

Cancer in your childbearing years

Many women with cancer are diagnosed at an age when they can have children. [Data from Italy](#) show they mainly have breast, gynaecological, and haematological cancers – leukaemias and lymphomas, as in Elena's case. "Leukaemia and lymphomas are the most frequent cancers in childhood, up to 20s–30s, while above 30–35 years of age the most common cancer among women is certainly breast cancer," says Fedro Peccatori, who heads up Fertility and Procreation in Oncology at the European Institute of Oncology in Milan.

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Thanks to timely and effective treatments, the great majority of these patients overcome the disease and still have their whole life ahead – a life which may include family plans. Women facing cancer increasingly consider the possibility of having children someday, and the prospect gives them a motivation to heal.

"When you discover the disease, as in my case, aged 30, what idea can better represent the future than the birth of a new life?" asks Marta. "It is a way to hold on to hope." Marta is an alias too. She and others who agreed to share their experiences are members of [aBRCAadabra](#), an association created to support carriers of BRCA genetic mutations, which predispose principally to breast and ovarian cancers.

An achievable goal

Today the plan to have a child after recovering from cancer can be achieved in a significant

proportion of cases, without major risks for the woman and her future children. Around 30%–50% of women who try for a child after breast cancer are successful, according to [a review](#) coordinated by Matteo Lambertini, at Policlinico San Martino, in Genova, with input from a wide range of specialists including Lucia Del Mastro also at the Policlinico San Martino, and Fedro Peccatori.

While the data show a 45% higher risk of preterm birth and a 50% higher risk of low birth-weight, they do not show a significantly higher risk of birth defects or complications during pregnancy or birth. Data on the risk of cancer recurrence after a pregnancy are reassuring too. “The latest international studies show that women with breast cancer who become pregnant after being treated for cancer, with the appropriate precautions and within the timeframe agreed with the oncologist and the expert gynaecologist, have a better prognosis than patients who decide not to have children, all other things being equal,” says Mariavita Ciccarone, president of Gemme Dormienti and gynaecologist at the San Carlo di Nancy Hospital in Rome.

Therapies that pose a risk to fertility

The risk posed to a woman’s ability to have children after cancer lies in certain anti-cancer drugs, which may be lifesaving but are also toxic to ovaries. “Chemotherapies are cytotoxic, they damage cells by altering their DNA, particularly drugs belonging to the class of alkylating agents, which are included in the majority of therapeutic regimens,” says Lambertini.

“Women who wish to leave open the possibility of pregnancy after healing should think about it before therapy and protect their ovaries and oocytes”

By attacking DNA, alkylating agents induce suicide of rapidly multiplying cells, which include cancer cells, but also other tissue, such as bone marrow, hair follicles and ovaries. “Other weapons used to treat some types of breast cancer are hormonal drugs, which are effective against tumours whose growth is stimulated by hormones,” says Lambertini. “Hormonal drugs have no toxic effects on the ovaries, but they are teratogenic: if a pregnancy starts while taking the drugs it can result in birth defects. Therefore, as long as a patient is on hormone therapy, she shouldn’t try to get pregnant, and usually the therapy lasts 5–10 years.

“Meanwhile, the ovaries age, and the likelihood of being able to conceive spontaneously at the end of the treatment decreases. So, women who wish to leave open the possibility of pregnancy after healing should think about it before therapy and protect their ovaries and oocytes.”

Protecting the ovaries and preserving fertility

How can you protect the ovaries from the toxic action of chemotherapy? “By putting them to rest, using drugs that temporarily and reversibly suspend their activity – so-called GnRH analogues,” explains Lambertini. “Given by intramuscular or subcutaneous injection once a month, they induce a temporary pharmacological menopause while receiving chemotherapy.” In this way, ovaries can regain their ability to produce oestrogen and progesterone once the effect of the pharmacological menopause has ended.

Avoiding definitive early menopause in this way also has important general health benefits, which include protecting against increased cardiovascular risk and bone calcium loss. However, GnRH

analogues are not quite as effective for preserving the integrity of oocytes and therefore fertility, says Lambertini. “At the end of the treatment, the ovaries are more likely to return to activity, with the menstrual cycle being resumed, but it is not certain that the woman will still be fertile, as her eggs may have been damaged. The only way to guard against this problem is to induce the maturation of some oocytes and freeze them before starting chemotherapy, to attempt assisted conception after recovery, or to freeze portions of ovarian tissue that can be implanted again after recovery to produce mature oocytes.”

“Protection of the ovaries with GnRH analogues is not an alternative to cryopreservation of oocytes or ovarian tissue”

It is important to be clear that protection of the ovaries with GnRH analogues is not an alternative to cryopreservation of oocytes or ovarian tissue, he emphasises. “On the other hand, even the woman who has secured a reserve of oocytes for possible future use should avoid premature menopause and the damage to general health that this entails.”

Freezing ovarian tissue is a more recent technique than freezing mature oocytes and it still does not guarantee the same chances of success. For this reason, today it is reserved for patients who receive a cancer diagnosis before puberty, when it is impossible to stimulate oocytes maturation, or when there is no time, because of the urgency of starting cancer therapy. “A couple of days is enough to organise ovarian tissue harvesting,” explains Lambertini, “while it takes about two weeks to stimulate the maturation of an adequate number of oocytes and collect them. Usually, a woman who receives a diagnosis of breast cancer has a few weeks before starting chemotherapy, so she can undergo ovarian stimulation and oocytes collection, but of course the fertility preservation team has to work in concert with the oncology team to avoid delays.”

Virtuous paths, tortuous paths

Some women, like Giorgia, another member of aBRCAadabra, are lucky enough to find themselves in a well-organised system. “The oncologist I trusted spoke to me on the very first day about the option to preserve my fertility and arranged an appointment at the assisted reproduction centre in the same hospital just two hours later,” she says. “I immediately started the process to collect the eggs, and later the treatment to induce a pharmacological menopause to preserve ovarian function. My need to still be a woman and the timeframe imposed by urgent therapy were both respected.”

“This is exactly what should happen in the ideal situation,” says Peccatori. “After the diagnosis, the woman should receive advice from the oncofertility expert, not necessarily a doctor but a nurse or counsellor, who can explain the options, and the success rates in relation to the woman’s age, her wishes and her therapeutic plan – because not all therapeutic plans have the same toxicity. If her wish is to access fertility preservation, she should immediately be referred to a public MAP [medically assisted procreation] centre, where she can receive ovarian stimulation for the collection and storage of oocytes, or undergo ovarian tissue harvesting.”

Telemedicine also works for reproductive medicine. We need to bring information and advice to as many women as possible”

As Elena told us, however, it doesn't always work like that. Sometimes specific advice is lacking, or information is given too late. "At the moment this remains the main bottleneck, but there would be a fairly simple way to solve it, which paradoxically the Covid-19 pandemic taught us," says Peccatori. "Over the last year we learned that telemedicine – the possibility to visit and counsel by means of digital platforms – also works for reproductive medicine. We need to make an effort to optimise the results we have already achieved, to bring information and advice to as many women as possible."

At other times, patients are correctly informed about options, but they are not supported to take the next steps. "The task of coordinating cancer and fertility care should not be left to the patient, who is usually going through a difficult time, coming to terms with their diagnosis and disoriented by the maze of the health system," says Annalisa, another voice from aBRCAdabra. In some areas of Italy, especially in the South, these difficulties are exacerbated by the lack of public assisted reproduction centres, as almost all facilities are private.

We urgently need to implement the integrated diagnosis and assistance paths, as mandated in a directive from the Italian Ministry of Health on assistance to cancer patients who wish to preserve their fertility, which was approved in 2019 by the State-Regions Conference. Each Region is called on to implement and organise its own path, but very few have done so up to now. Among the most advanced is Lazio. All oncologists in this region are required to inform women of childbearing age at the time of diagnosis about the possibility to preserve oocytes, and to refer interested patients to the Regional Reference Centre for oocyte cryopreservation at the Sandro Pertini Hospital in Rome.

"Here we see a patient within 72 hours of the oncologist's call and immediately do the tests to evaluate her ovarian reserve and the feasibility of preservation," explains Rocco Rago, director of the Lazio Regional Reference Centre. "Ovarian stimulation can be started on any day of the natural cycle, and the whole procedure, up to the oocytes collection, lasts 10–12 days. If there is more time available, the stimulation can be repeated and more eggs collected to increase the chances of success when the woman tries to become pregnant."

Embryo freezing

There is another option – viable in other countries, but not accessible in Italy by law. This is to stimulate the ovaries, collect mature oocytes, fertilize them with sperm from the woman's partner and freeze the embryos instead of the oocytes.

According to Giulia Scaravelli, head of the National MAP Register of the Italian National Health Institute, that option could offer a higher chance of success and could be offered to younger women with a better prognosis. "The benefits of embryo cryopreservation in the general population are well known, including its relatively high success rate and the existence of well-tested protocols," she says. The [latest available data](#) from the National MAP Register, relating to 2018, agree: there is around a 30% success rate of pregnancies from cryopreserved embryos versus 17% of pregnancies obtained from cryopreserved oocytes.

Not surprisingly, the 2020 [guidelines from ESHRE](#) (the European Society of Human Reproduction and Embryology) and [from ESMO](#) (the European Society for Medical Oncology) state that, in addition to the option of cryopreserving unfertilized oocytes, women with a partner should be offered the option to also try cryopreservation of embryos, using half of the collected oocytes. In Italy, however, this cannot be done, due to restrictions on embryo freezing imposed by law 40/2004 regulating medically assisted procreation. As recent [guidelines from AIOM](#) (the Italian Association of Medical Oncology) point out, Italian law allows only couples with proven infertility to access in vitro fertilisation. "In my opinion a patient on the brink of undergoing cancer treatment is in fact infertile," says Scaravelli.

Risk, actual and perceived

Fears among patients, and even some doctors, that ovarian stimulation could compromise the cancer prognosis, has been a deterrent against opting for fertility preservation, particularly for women with tumours sensitive to sex hormones.

“My breast surgeon told me he was against cryopreservation; he advised it was too dangerous for me. This frightened me a little,” says Nicoletta. “What’s more, I felt out of place, as if I was crazy to have other thoughts besides saving my life.”

“The data show that ovarian stimulation does not increase the risk of recurrence even for hormone-responsive tumours”

“Over the past five years a series of very reassuring data has been published,” Peccatori responds ([J.Kim et al. *J Clin Endocrinol Metab*, 2016](#); [A.Rodriguez-Wallberg et al. *Breast Cancer Res Treat*, 2018](#); [A.Marklund, PhD thesis, Karolinska Institute, 2021](#)). “They show that ovarian stimulation does not increase the risk of recurrence even for hormone-responsive tumours. Of course, there may be areas that still need research, for example there is discussion about how safe it is to do ovarian stimulation in women who still have the tumour in place and have to undergo preoperative (neoadjuvant) chemotherapy to decrease the size of the tumour before surgery. In general, however, I believe the issue of safety of the stimulation, when it is performed with *ad hoc* protocols, is outdated.”

Women with a cancer predisposition

Preservation of oocytes does not worsen the prognosis even for women with BRCA mutations. “In addition to breast cancer, some of them are also predisposed to ovarian cancer,” explains Alberta Ferrari, breast surgeon at the IRCCS Policlinico San Matteo Foundation in Pavia. “Therefore, these women are recommended to have the ovaries and fallopian tubes removed between 35 and 45 years of age, depending on the individual risk. Those who want to have children should plan pregnancies before the age of 35, or preserve the oocytes to be used later. Egg storage is particularly recommended to women who are diagnosed with breast cancer and then discover that they are carriers of a BRCA mutation, but even healthy women who know they are carriers should have the opportunity to preserve the eggs, in view of a preventive removal intervention.”

“ABRCAdabra wants to see reimbursement of oocyte preservation extended to healthy carriers of the BRCA mutation”

In Italy, oocyte preservation for a healthy woman who plans a preventive intervention is not currently reimbursed by the National Health Service. ABRCAdabra, which includes among its members both healthy carriers and carriers with a cancer diagnosis, wants to see reimbursement extended to healthy carriers of the BRCA mutation. “Cryopreservation of ovarian tissue, on the other hand, is not recommended to carriers of BRCA mutations, because there is a significant risk that the frozen tissue would contain cancer cells,” says Ferrari.

Egg preservation offers an additional benefit to women with a BRCA mutation, adds Lambertini. "When trying to get pregnant, they can submit the embryos produced with stored oocytes to pre-implantation diagnosis, and implant only those that have not inherited the mutation." But again, you first need to know about the options.

"I didn't want to risk my children inheriting my mutation – the one that took my mother, grandmother and cousin away from me," says Sara, another member of aBRCAclub, "that's why I reluctantly decided not to preserve fertility. In general I am satisfied with all the information received on cryopreservation. The only thing that was omitted, or maybe I missed it due to stress after the diagnosis, is that the transmission of the mutated gene can be avoided."

Women's choices

What do women of childbearing age who are diagnosed with breast cancer want? How do they face the prospect of preserving fertility in view of possible future pregnancies? How many are interested in egg cryopreservation? And those who give up, why do they do it? To answer these questions, Lambertini and colleagues started the [PREFER-FERTILITY study](#), enrolling newly diagnosed women aged 18 to 45, with early-stage breast cancer and therefore with good prospects for recovery.

"More than 90% of the volunteers said they were concerned about the risk of premature menopause due to chemotherapy," says the oncologist, summing up the preliminary results of the research. "90% decided to take GnRH analogues to avoid chemotherapy-induced early menopause. More than 30% consulted the gynaecologist to decide on the possible oocyte preservation, but only just over 10% took that path. The main reason for declining the offer to preserve fertility was the desire not to have children or not to have more children. Among those who would have wanted children, those who refused cryopreservation did so mostly for fear that ovarian stimulation and the possible delay of chemotherapy to collect the oocytes would worsen the cancer prognosis. Others refused fertility preservation to avoid a demanding treatment in the face of relatively low probability of success of a future pregnancy with frozen oocytes, which is between 20% and 50% depending on the woman's age."

"Of course," Ciccarone acknowledges, "preserving does not mean having the 100% guarantee of a child, because no human being is absolutely certain to procreate. Preserving, however, means setting aside a treasure that can be useful when needed, that is, after healing."

In Italy, the numbers benefiting from fertility preservation are still low, but they represent a timid positive sign. Published data show there have been 15 pregnancies and nine babies born from oocytes cryopreserved from cancer survivors in Italy, so far, as well as five pregnancies and three babies born from cancer survivors' cryopreserved ovarian tissue, says Scaravelli. "It must be said, however, that the number of births is increasing," she adds, "and that oocytes and tissue cryopreservation is a novel technology: a lot of women who did it haven't yet come back to use those cells and tissue."

A well-informed woman has the tools to decide in full awareness, whether her choice is a yes, or a no, like Renata's. "The oncologist told me about egg storage, but I wasn't interested," she says. "Children were no longer in my head, I am 40 years old... A few days later I went to the general practitioner, who also told me about this option. The oncologist then reiterated it to me before starting chemo. In short, they verified in every way that it didn't interest me."

"It should be doctor's job to inform the young patient and assist

her”

“There are women who are reluctant because they are not well informed, others who come to the oncologist already with a fertility preservation plan. It should be doctor’s job to inform the young patient and assist her,” says Peccatori.

“Today there is much more attention and awareness of oncofertility than in the past,” says Lambertini. “All national and international guidelines say that the doctor must address the issue with the patient. If they do not, and the uninformed woman loses the possibility of having children, the doctor risks legal consequences too. Nevertheless, it is still possible to come across a careless physician, and so we must go on raising awareness, not only among health professionals but also among patients.”