RBMO

COMMENTARY

Fertility preservation before sterilizing treatment: cryopreservation of both ovaries to restore endocrine and reproductive functions

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ABSTRACT

Ovarian cortex cryopreservation is now a validated fertility preservation technique. Autotransplantation of this tissue allows restoration of ovarian hormone function in more than 90% of patients, and birth of at least one child in 30% of transplanted women. In the case of very highly gonadotoxic treatments, it is recommended that ovarian cortex be cryopreserved as first-line therapy to safeguard future fertility. However, the ovary left in place runs a very high risk of being significantly altered. This raises the question of harvesting both ovaries, looking to restore fertility as well as endocrine function. Indeed, hormone balance in these cancer survivors may be recovered naturally for their entire lifetime. Autotransplantation could also be performed to restore hormone function in women with no wish to have children, with the sole purpose of improving their quality of life. Ethical and legal challenges exist and are discussed in this paper, but they do not constitute an argument against it. Clinical trials investigating this strategy are clearly needed, but this approach truly offers women the chance of having both endocrine and reproductive functions restored and maintained throughout their entire life.

INTRODUCTION

The two functions of the ovary, namely procreation and hormone activity, are linked to the same structure, the ovarian follicle, and are completely inseparable. Transplantation of cryopreserved ovarian tissue allows restoration of ovarian hormone function in around 90% of cases, and the birth of at least one child in 30% of transplanted women (*Dolmans et al., 2021*). Recommendations state that ovarian tissue removal for fertility preservation is indicated as first-line therapy when treatments are highly gonadotoxic (*Rives et al., 2022*). However, if the required therapy is highly gonadotoxic, there is a great risk that the remaining ovary will also be severely altered. Indeed, it is likely that the patient will experience premature ovarian insufficiency upon or very soon after completion of treatment.

In the context of fertility preservation, teams currently harvest between a half and one whole ovary, and ovarian tissue transplantation mainly serves to enable women to have children. At present, there are insufficient data on the number of fragments or proportion of ovarian tissue needed to obtain at least one birth. Nevertheless, it is known that the number of ovarian fragments transplanted correlates with the chances of pregnancy: the more fragments grafted, the higher the chances of pregnancy (*Poirot et al., 2019*).

Ovarian tissue transplantation aiming to restore only endocrine function of the ovary could allow these patients to avoid taking hormones to induce puberty and/or replace hormone replacement therapy (HRT) in adulthood. However, there are no reliable a priori parameters for predicting the duration of ovarian graft function. The largest published series of ovarian tissue transplantations based on individual data showed that, at 5 years, 55% of grafted patients still had ovarian function (*Dolmans et al., 2021*).

In this context, is it possible to use ovarian fragments to restore ovarian hormone function regardless of the wish to conceive? Given the uncertainties mentioned above, it is usually preferable to

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Declaration: The authors report no financial or commercial conflicts of interest.

KEY WORDS
Fertility preservation
Ovarian hormone function
Ovarian tissue cryopreservation
Ovarian tissue transplantation
Pregnancy

keep all cryopreserved ovarian fragments to give patients the best chance of having at least one child.

Finally, in order to restore both ovarian functions within a different time frame with sequential ovarian fragment autotransplantations, is it possible to propose the removal of both ovaries in the case of highly gonadotoxic treatment? More ovarian tissue would then be available, making it possible to restore both reproductive and endocrine functions at different points in time, and even boost the chances of pregnancy by increasing the number of grafted ovarian fragments (and more transplantation procedures). What could be the medical benefits of harvesting and using both ovaries, and is this ethically and legally feasible? The current authors have attempted to address these questions.

ETHICAL ASPECTS

In addition to research, exploratory discussions guided by biomedical ethics principles were conducted by clinical ethics consultants with 14 healthcare professionals (6 haematologists or oncologists including 4 paediatricians, 2 biologists, 2 surgeons and 4 assisted reproduction doctors) as well as three patients who had each had two children after removal, freezing and subsequent grafting of one ovary prior to highly gonadotoxic treatment. Women who had had only one child or none at all were excluded to avoid any risk of malfeasance (to avoid a situation where these patients would regret or allocate blame for the lack of a proposal to freeze both their ovaries). A multidisciplinary discussion then took place with 15 individuals trained in clinical ethics (among them 5 medical doctors, 2 paramedics, 2 psychologists, 1 philosopher, 1 jurist and 1 sociologist). The findings are presented here to provide some food for thought.

Futility — Removing both ovaries may seem futile, as the removal of one already appears technically complex, with serious consequences for hormone function. Moreover, ovarian cortex transplants are rarely carried out in the end (because of being either not recommended or not requested).

Uncertainty — Most professionals reject the idea of removing both ovaries due to scientific uncertainty. According to some, the lifespan and efficacy of ovarian grafts are still unpredictable, and fertility may endure naturally after highly gonadotoxic treatment.

Symbolic significance — In the view of professionals, infringement upon physical integrity, especially since the reproductive organs are involved, appeared to be the strongest argument against removing both ovaries, evoking the idea of intentional castration.

Hormonal function — For haematologists and oncologists for the most part, preservation of endocrine function cannot assume the same importance as preservation of fertility.

Informed consent — Last but not least, doctors are concerned about how and when to inform patients and obtain consent to remove both ovaries from sick and vulnerable patients, especially minors (and their parents).

Nevertheless, a number of counterarguments were identified.

Beneficence — Everything associated with the preservation of fertility during cancer care looks to be very welcome from the patients' point of view, because it relates to their future and gives them hope. Furthermore, removing two ovaries instead of one is not technically very different, and sequential ovarian fragment autotransplantations may offer drug-free options in later life (no hormone treatments, no assisted reproduction). Specific medical data on the cancers and treatments involved, combined with the impact of patient age, can also help to identify contexts where it appears more opportune to remove both ovaries.

Non-maleficence — None of the patients mentioned 'castration'; instead they provided a different view of what they deemed 'natural', namely living without hormone treatments and avoiding assisted reproduction. In their opinion, and that of several doctors, taking two ovaries in order to preserve natural endocrine function was as acceptable as fertility preservation in terms of its long-term impacts on comfort and quality of life.

Respect for autonomy — While not all of the three patients interviewed would have (hypothetically) agreed to have both ovaries removed, they felt that the women involved should be informed so they can decide for themselves. Professionals also emphasized respect for autonomy, despite difficulties related to informed consent.

Justice — As the law evolves, opening up avenues for the preservation of hormone function, the medical profession is once again facing questions about sexual health. These issues, linked to intimacy and identity, cannot be resolved in an exclusively medical setting, inviting a broader societal discussion. In particular, women must have their say.

LEGAL ASPECTS

Removing two ovaries could be likened to surgical castration, but in France as in other countries around the world, surgical castration is illegal. Are there any legal arguments against removing both ovaries from women who have undergone or are due to undergo treatment that could lead to infertility, and then freezing the organs for subsequent transplantation? While this procedure ultimately restores both aspects of ovarian function, fertility and endocrine activity, it actually eradicates all fertility until transplantation is carried out.

In France, the bioethics law passed on 2 August 2021 extended the purposes for which germ cell tissue retrieved and preserved as part of such medical treatment may be transplanted. *Restoration of hormone function* is legally permitted (*French public health code*, art. L 2141-11). Indeed, beyond pregnancy, ovarian tissue transplantation restores endocrine function and secretion of hormones, enhancing quality of life for many women.

A legal analysis of this reveals three statements of fact:

- This is not castration. Under French criminal law, castration is prosecuted on the basis of ordinary offences against the person. In this case, the objective is medical and the purpose specific.
- This is not sterilization. Sterilization, provided for under the *French Public Health Code* (French public health code, art. L 2123-1), involves tying the Fallopian tubes or vas deferens.
- The procedure in question is more akin to removal of the uterus from a living donor, with a view to transplanting it to a recipient for maternity purposes, rendering the donor sterile. Now permitted and practised, this must

comply with the provisions of the Public Health Code on the donation and use of constituents and products of the human body (*French public health code*, art. L 1211-1 to L 1274-3). The procedure, which results in total sterility for any living woman donating her uterus, is not disputed in law.

From a legal standpoint, removing both ovaries with a view to transplantation does appear to comply with the law. However, there are a number of conditions that must be met for such a procedure to be legitimate, and these have been reinforced by the aforementioned bioethics law.

- The first condition concerns providing adequate information and obtaining patient consent. This information must be all the more detailed when the sample covers both ovaries.
- If the sample is taken for medically assisted reproduction purposes, the age of the person is now set by law (*French public health code*, art. R 2141-36). A sample may be taken from a woman up to her 43rd birthday.
- Finally, the law also stipulates that the individuals involved must be regularly asked about the fate of their stored samples (*French public health code*, art. L 2141-11).

MEDICAL ASPECTS

Girls at extremely high risk of completely losing their ovarian function due to sterilizing treatment might wish to consider freezing both ovaries. Indeed, ovarian tissue transplantation is usually performed giving absolute priority to reproductive function when limited amounts of tissue are available. If both ovaries are frozen, the aim of ovarian tissue transplantation would be to restore the hypothalamic–pituitary–ovarian axis that would allow physiological pubertal development and maintenance of reproducible concentrations of endogenous ovarian hormones until menopause. The main medical advantage of this procedure is the possibility of restoring the hormonal balance throughout a woman's entire life after she is cured, enabling better cardiovascular, cognitive and bone health. Endocrine restoration would be particularly useful for two specific stages: puberty induction and menopause-related symptom relief.

Puberty induction

Spontaneous puberty rates after highly gonadotoxic treatments, such as myeloablative conditioning prior to allogeneic haemopoietic stem cell transplantation, range from less than 15% to 40% (*Chabut et al. 2023*; *Leiper et al. 2020*; *Weinhard et al. 2020*). Puberty induction in hypogonadal girls involves the daily application of transdermal 17β-oestradiol patches for at least 1 year, starting at a median dose of 0.14μg/kg per day and increasing every 6 months. Oestrogens such as 17β-oestradiol are the dominant formulations currently used and are favoured over non-natural alternatives such as ethinyl oestradiol or conjugated equine oestrogens. However, the optimal type, route of administration and dose for puberty initiation are not well established. Progestogens are typically introduced after 2–3 years of oestrogen therapy, but there is no universal consensus on the age at which to begin treatment in patients with known hypogonadism (for example, after chemotherapy). Nevertheless, many consider 11–12 years to be the most appropriate age.

Reimplanting ovarian tissue to induce puberty at the age of 11–12 years may represent a better option than the daily intake of oestrogens in the long term, as the hypothalamic–pituitary axis can regulate ovarian secretion from the transplant more naturally (*Poirot et al., 2012*). Concordance and self-regulation should be considered as advantages of this technique.

Menopausal symptoms

According to the literature, the risk–benefit balance of HRT use in healthy women aged 50–59 years, or within 10 years of menopause, shows lower rates of all-cause mortality, without any increase in breast cancer. Of course, young cancer survivors who see their ovarian reserve completely depleted by aggressive chemo- or radiotherapy share the same oestrogen-deprived status.

Restoration of ovarian endocrine function through reimplantation of frozen-thawed ovarian tissue could prevent menopause-related conditions, such as osteoporosis and other disorders resulting from oestrogen deprivation. Several authors have indeed demonstrated ovarian activity and progesterone secretion after grafting of human ovarian tissue, with long-term endocrine function that could persist for more than 7 years and even 12 years with a repeat procedure. If the goal is restoring endocrine function but not fertility, a heterotopic location (namely outside the pelvic cavity, such as the abdominal wall) can be used, which is less invasive and potentially achievable under local anaesthesia.

Advantages of this technique include psychological relief, as taking daily pills reminds cancer survivors every day of their previous disease, which is a burden they carry all their life. Moreover, it would allow young girls to consider their menstrual cycle 'natural', as patients very often prefer to 'menstruate by themselves'. In these conditions, frozen-thawed tissue transplantation solely to restore endocrine function would stop the girl feeling any different from her schoolfriends, an important issue for adolescents.

One drawback of this approach is that it leaves no possibility for the natural resumption of ovarian activity in the remaining ovary. Notwithstanding, after ovarian tissue autotransplantation, the rate of restoration of hormone function is around 90% and the percentage of women giving birth to at least one child around 30%. These results are markedly higher than what can be expected after natural resumption of ovarian function.

Clinical trials investigating this approach are clearly needed, but we should bear in mind that most natural oestrogens are produced by the ovary itself, not by a pharmaceutical company. Both medical and ethical concerns should be fully addressed before proposing the removal of both ovaries (especially in specific categories of cancer patients). Nevertheless, this offers women who are cured the chance of having both endocrine and reproductive functions restored and maintained throughout their entire life.

DATA AVAILABILITY

No data were used for the research described in the article.

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Received 29 May 2024; received in revised form 27 August 2024; accepted 27 September 2024.