Reproductive BioMedicine Online

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

--Manuscript Draft--

Manuscript Number:	
Article Type:	Commentary
Section/Category:	Reproductive endocrinology and health
Keywords:	fertility preservation; ovarian tissue cryopreservation; pregnancy; ovarian hormone function; ovarian tissue transplantation
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Abstract:	Ovarian cortex cryopreservation has become a validated fertility preservation technique. Ovarian tissue autotransplantation (OTT) allows restoration of ovarian hormone function in around 90% of cases, and the birth of at least one child in 30% of transplanted women. In the case of highly gonadotoxic treatments, it is recommended that ovarian cortex cryopreservation for fertility preservation, be offered as a first-line treatment and it is also in this case that the ovary left in place has a very high risk of being significantly altered. The question of harvesting both ovaries could be raised, in order to restore both the hormonal function of the ovary and fertility, but in a different timeframe, and in particular to be able to perform OTT only to restore hormonal function without any wish to have children. Of course, there are ethical and legal issues involved, but neither of these is an argument against it. Clinical trials investigating this approach are cleary needed. Nevertheless, this offers the women chance of having both endocrine and reproductive functions restored and maintained througout their entire life.
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Université catholique de Louvain
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UCL Université catholique de Louvain

Brussels, May 29, 2024

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Juan Antonio García Velasco
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Dear Juan,
Dear Nick,

I would like to send our Commentary entitled 'Fertility preservation before sterilizing treatment: cryopreservation of both ovaries to restore endocrine and reproductive functions'.

This is a short manuscript with provocative idea that I believe is worth considering for publication in your journal as the topic is exactly related to the field of RBMonline.

Sincerely yours,

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

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

Key words: fertility preservation, ovarian tissue cryopreservation, pregnancy, ovarian hormone function, ovarian tissue transplantation

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 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 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 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 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 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 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, could we propose removal of both ovaries in 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? We have attempted to address these questions.

ETHICAL ASPECTS

The clinical ethics center (Assistance Publique - Hôpitaux de Paris) set out to explore these ethical issues. Two clinical ethics consultants (a medical doctor and psychologist or lawyer) interviewed 14 healthcare professionals, including 6 hematologists or oncologists (including 4 pediatricians), 2 biologists, 2 surgeons and 4 doctors working in assisted reproduction. They also met 3 patients who had had 2 children after removal, freezing and subsequent grafting of one ovary prior to gonadotoxic treatment. Interviews focused on the hypothetical possibility of removing both ovaries. Ethical issues around ‘medicalization’, ‘uncertainty’, ‘symbolic significance’, ‘hormone function’ and ‘information’ emerged.

Medicalization. Removing both ovaries may seem futile, as removal of one already appears technically complex, with serious consequences on hormone function. Moreover, ovarian cortex transplants are rarely done in the end (not recommended or not requested). **Uncertainty.** Most professionals reject the idea of removing both ovaries due to scientific uncertainty. The lifespan and efficacy of ovarian grafts are still unpredictable according to some, and fertility may endure naturally after gonadotoxic treatment. **Symbolic significance.** Infringement upon

physical integrity, especially since reproductive organs are involved, appeared to be the strongest argument against removing both ovaries in the view of professionals, evoking the idea of intentional castration. **Hormonal function.** For hematologists and oncologists for the most part, preservation of endocrine function cannot assume the same importance as preservation of fertility. **Information.** 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 from an ethical perspective.

Beneficence. Everything associated with 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 very different technically and may offer drug-free option 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' and 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 three patients interviewed would have (hypothetically) agreed to have both ovaries removal, they felt that 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 avenues for 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. Women in particular must have their say.

LEGAL ASPECTS

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 August 2, 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.

1) This is not castration. Under French criminal law, castration is prosecuted on the basis of ordinary offenses against the person. In this case, the objective is medical and the purpose specific.

2) 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.

3) 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 practiced, it must comply with provisions of the Public Health Code on 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 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 subjects involved must be regularly asked about the fate of their stored samples (French public health code, art. L 2141-11).

One final question emerges from this legal analysis. Would a woman have the right to demand that a team take such a sample for the purposes of freezing and subsequent transplantation? Can the benefits of medical progress become a right? The answer is no. There can be no demand to take advantages of medical advances at any price. Nevertheless, comprehensive information and clear and thorough explanations are likely to prevent any unwarranted requests.

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, there will be enough to also contemplate

transplantation for endocrine function purposes, namely puberty induction and HRT. 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. Endocrine restoration would be particularly useful for two specific stages: puberty induction and menopause-related symptom relief.

- **Puberty induction** (Poirot *et al.*, 2012)

A large series on childhood cancer survivors published by Chabut et al. (2023) (n=178 women: 116 with total body irradiation and 62 with a busulfan-based conditioning protocol) reports that 60% of subjects needed puberty induction, and this figure climbed to >85% if the patient underwent hematopoietic stem cell transplantation after the age of 10.9 years.

Puberty induction in hypogonadal girls involves daily application of transdermal 17-β-estradiol patches for at least 1 year, starting at a median dose of 0.14 µmg/kg/day and increasing every 6 months. Estrogens like 17-β-estradiol are the dominant formulations currently used and are favored over non-natural alternatives like ethinyl-estradiol or conjugated equine estrogens. 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 estrogen therapy, but there is no universal consensus on the age at which to begin treatment in patients with known hypogonadism (like after chemotherapy). Nevertheless, 11-12 years is considered by many as the most appropriate age.

Reimplanting ovarian tissue to induce puberty at the age of 11-12 years may represent a better option than daily intake of estrogens for the long term, as the hypothalamo-hypophysis axis can regulate ovarian secretion from the transplant more naturally. Compliance 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 estrogen-deprived status.

Restoration of ovarian endocrine function through frozen-thawed ovarian tissue reimplantation could prevent menopause-related conditions, such as osteoporosis and other disorders resulting from estrogen 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, like the abdominal wall) can be used which is less invasive and potentially achievable under local anesthesia.

Advantages of this technique include psychological relief, as taking daily pills reminds cancer survivors of their previous disease every day, 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.

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

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