RBMO

COMMENTARY

Ovarian tissue cryopreservation in breast cancer patients: glass half empty or glass half full?

Claus Y. Andersen[1,2,*], Jacques Donnez[3], Erik Ernst[4], Debbie Gook[5], Antonio Pellicer[6], Michael Von Wolff[7], Nao Suzuki[8], Christophe Roux[9], Marie-Madeleine Dolmans[10]

ABSTRACT

This is a commentary to a paper recently published in *RBMOnline* by Macklon and De Vos, in which they argue for a discontinuation of ovarian tissue freezing for fertility preservation in women with breast cancer. Instead, they suggest the use of oocyte vitrification following ovarian stimulation as the preferred method of fertility preservation. This commentary presents nine separate arguments that should be considered in the context of ovarian tissue freezing and fertility preservation in girls and women. Collectively, the authors support ovarian tissue freezing going forward and suggest continuing this procedure for fertility preservation in women with breast cancer. Ovarian tissue freezing represents several advantages for patients and provides them with more options following treatment compared with oocyte vitrification.

We read with interest the recent paper by Macklon and De Vos, in which they express their views on fertility preservation in breast cancer patients and the approach that should be taken going forward (*Macklon and De Vos, 2024*). They suggest that ovarian tissue cryopreservation (OTC) be abandoned and replaced with ovarian stimulation and cryopreservation of mature oocytes in these individuals. This notion is primarily based on information that OTC invariably leads to iatrogenic depletion of the ovarian reserve in affected women and that fertility, pregnancy and delivery rates in younger breast cancer survivors are reassuringly high, even after chemotherapy.

We would like to express a different and more nuanced opinion on the general outlook for these women who wish to maintain their fertility. Indeed, we are much more optimistic and feel that the authors' views reflect a glass half empty rather than a glass half full. These views can be raised point by point:

1. Clearly, fertility preservation by freezing ovarian tissue may theoretically constitute an iatrogenic reduction of the ovarian reserve, as the excised tissue is frozen for patients to use later in life. This does not differ from any other indication for OTC, but implies a certain scepticism towards the procedure. Conversely, the current authors believe it is a great opportunity for young girls to safeguard their fertility for the future, helping young girls and women worldwide.

Furthermore, several investigations have now shown that the removal of one ovary does not compromise fertility or advance the age of menopause by more than 1 or 2 years (*Lass et al., 1997*; *Yasui et al., 2012*). It is even less likely when only one-third of each ovary is removed (*Donnez and Dolmans, 2017*), although long-term follow-up is required to assess future fertility.

2. Instead of performing ovarian stimulation and collecting mature oocytes, cortical tissue freezing is a valid option in these patients. Immature oocytes from the medulla should also be matured *ex vivo*, so

KEY WORDS

Fertility preservation
Ovarian tissue cryopreservation
Oocyte vitrification

[1] The Fertility Clinic, Copenhagen University Hospital Herlev, Herlev, Denmark
[2] Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[3] Université Catholique de Louvain and Society for Research into Infertility (SRI), Brussels, Belgium
[4] University Clinic for Fertility, Regional Hospital Horsens, Horsens, Denmark
[5] Reproductive Services, The Royal Women's Hospital, and Department of Obstetrics and Gynecology, University of Melbourne, Parkville, Victoria, Australia
[6] IVIRMA-Global, IVI Rome, Valencia University School of Medicine, Valencia, Spain
[7] Division of Gynecological Endocrinology and Reproductive Medicine, University Women's Hospital, University of Bern, Inselspital Bern, Switzerland
[8] Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, Kawasaki, Japan
[9] Assisted Reproductive Technologies Department, INSERM CIC 1431, University Hospital, Besançon, France
[10] Gynaecology Research Unit, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium

*Corresponding author. E-mail address: cya@yding.com (C.Y. Andersen). https://doi.org/10.1016/j.rbmo.2024.104442 1472-6483/
Declaration: The authors report no financial or commercial conflicts of interest.

patients can potentially benefit from both sources for subsequent fertility restoration. The in-vitro maturation procedure is an experimental procedure but currently undergoing rapid development. During a recent Ovarian Club Meeting in Paris it was suggested that now is the time to offer both these procedures for fertility preservation purposes. Indeed, the collection of immature oocytes often results in as many metaphase II oocytes after in-vitro maturation as ovarian stimulation is likely to generate.

3. Furthermore, Macklon and De Vos claim that 'Despite its widespread use, few women come back to make use of their cryopreserved tissue', highlighting that the number of patients actually returning for ovarian tissue transplantation (OTT), as reported, is limited. However, the frequency with which patients return for OTT is the central figure to examine when breast cancer is compared with other diagnoses in the context of OTC. The authors fail to reference a study (with Macklon as co-author) from 2019 (*Kristensen et al., 2021*), which reported that former breast cancer patients generally returned just as often as other cancer sufferers, amounting to around 1 in 5 patients undergoing OTC in the evaluated group. This clearly contradicts the statement by Macklon and De Vos that only a small number of breast cancer patients come back for OTT.

In fact, the numbers of patients returning for OTT should be compared with the numbers returning after oocyte vitrification with similar diagnoses. The rate is low irrespective of the method, but robust data are lacking. Macklon and De Vos use this argument to propose oocyte vitrification instead of OTC, but implementation rates for both techniques are much alike. We do not therefore find this argument convincing in terms of stopping OTC and switching to oocyte vitrification in breast cancer patients. Furthermore, the surgical procedure used for OTC is safe, with a very low frequency of side effects reported.

4. The Danish study (*Kristensen et al., 2021*) claims that some breast cancer patients experience a severe decline in their ovarian reserve during cancer therapy and subsequent difficulty in achieving a pregnancy, despite not being menopausal. They can then return to boost their ovarian reserve through OTT and enhance their chances of conception (*Dolmans et al., 2021*). From the patient's perspective, it is irrelevant whether the oocyte that is eventually fertilized and results in a child derives from in-vivo tissue or transplanted tissue. Both oocytes are her own.
5. If a patient has undergone OTC for fertility preservation but does not wish to use her tissue for fertility purposes, which happens in many cases regardless of the methods applied, there is an alternative way for her to use it. A large proportion of women undergoing breast cancer treatment experience a serious drop in their ovarian follicle pool (irrespective of fertility preservation measures) and may run the risk of premature ovarian insufficiency. If young breast cancer patients with oestrogen-negative tumours undergo OTC rather than storing oocytes, they have the option of OTT later in life to postpone premature ovarian insufficiency and alleviate some menopausal symptoms they may otherwise experience.
6. If a patient has oestrogen-positive breast cancer, it is debatable whether it is prudent to apply stimulation with exogenous gonadotrophins and create supraphysiological oestrogen concentrations that could potentially stimulate the cancer. This effect can now be mitigated by using aromatase inhibitors such as letrozole during ovarian stimulation. Nevertheless, it still generates oestradiol concentrations around twice as high as those during a normal menstrual cycle, and whether this has an adverse effect on the cancer itself is not yet fully understood (*Poulsen et al., 2022*). Moreover, there are no large-scale studies evaluating outcomes in terms of live births in this specific group of breast cancer patients treated with letrozole.
7. In the case of the retrieval of mature oocytes after ovarian stimulation, the duration from referral to collection is around 14 days in the best-case scenario, while OTC is typically performed in under 5 days (in some centres only 3), which patients undoubtedly appreciate (*Donnez and Dolmans, 2017*).
8. Furthermore, there is usually time for only one attempt with ovarian stimulation. If it fails or a small number of oocytes are recovered, this is bad news for vulnerable patients, whose hopes are dashed. Indeed, fewer than four oocytes were collected from around 20% of women with cancer and the authors state that 'the risk of a weak response in breast cancer patients was 3 times higher than in non-Hodgkin's patients' (*Domingo et al., 2012*). This is in line with results from some of the current authors' clinics which have calculated that 25% of patients with a cancer diagnosis obtain fewer than 5 oocytes and 50% obtain fewer than 10 oocytes for fertility preservation following ovarian stimulation. Age and anti-Müllerian hormone concentrations are important parameters to guide the choice of procedure as the chances of a live birth depend on the number of oocytes available. Cobo and co-workers found that with five oocytes, the likelihood of a live birth was 15.4% in women aged under 36 years and 5.1% in those over 36 years (*Cobo et al., 2016*).
9. Breast cancer therapy is now developing into a more dynamic process, where the treatment of patients depends on their response to administered gonadotoxic drugs. If they do not respond sufficiently, the dose, and hence the gonadotoxic insult, may be increased. It is therefore crucial that patients undergo fertility preservation before the initiation of cancer treatment, irrespective of the fertility preservation approach (*Jadoul et al., 2017*). It is not advisable to perform ovarian stimulation once an individual has initiated cancer treatment. Indeed, previous studies clearly demonstrated poor outcomes when ovarian stimulation was performed during chemotherapy. In such cases, OTC is the only way of preserving fertility.

All in all, we believe that the implementation of OTC for fertility preservation in breast cancer patients is a step forward compared with oocyte vitrification, providing them with different options for use of their tissue, including fertility restoration and endocrine purposes. It must be acknowledged that doctors are more familiar with oocyte vitrification, a method that is widely known and represents standard practice. OTC, on the other hand, requires a different set-up, involving more teams with different expertise. However, in our view, OTC provides patients with alternatives, yielding

better utilization rates, so should absolutely remain a valid option for fertility preservation in breast cancer patients.

DATA AVAILABILITY

Data will be made available on request.

REFERENCES

Cobo, A, García-Velasco, JA, Coello, A, Domingo, J, Pellicer, A, Remohí, J., 2016. Oocyte vitrification as an efficient option for elective fertility preservation. Fertil Steril 105 (3), 755–764 PMID: 26688429.

Dolmans, MM, von Wolff, M, Poirot, C, Diaz-Garcia, C, Cacciottola, L, Boissel, N, Liebenthron, J, Pellicer, A, Donnez, J, Andersen, CY, 2021. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertil Steril 115 (5), 1102–1115 PMID: 33933173.

Domingo, J, Guillén, V, Ayllón, Y, Martínez, M, Muñoz, E, Pellicer, A, Garcia-Velasco, JA., 2012. Ovarian response to controlled ovarian hyperstimulation in cancer patients is diminished even before oncological treatment. Fertil Steril 97, 930–934 PMID: 22283969.

Donnez, J, Dolmans, MM., 2017. Fertility Preservation in Women. N Engl J Med 377 (17), 1657–1665 PMID: 29069558.

Jadoul, P, Guilmain, A, Squifflet, J, Luyckx, M, Votino, R, Wyns, C, Dolmans, MM., 2017. Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases. Hum Reprod 32, 1046–1054 PMID: 28333228.

Kristensen, SG, Wakimoto, Y, Colmorn, LB, Dueholm, M, Pors, SE, Macklon, KT, Mamsen, LS, Nikiforov, D, Cadenas, J, Greve, VH, Bay Bjørn, AM, Rosendahl, M, Pedersen, AT, Nyboe Andersen, A, Fedder, J, Ernst, E, Andersen, CY, 2021. Use of cryopreserved ovarian tissue in the Danish fertility preservation cohort. Fertil Steril 116, 1098–1106 PMID: 34130800.

Lass, A, Paul, M, Margara, R, Winston, RM., 1997. Women with one ovary have decreased response to GnRHa/HMG ovulation protocol in IVF but the same pregnancy rate as women with two ovaries. Hum Reprod 12, 298–300 PMID: 9070715.

Macklon, KT, De Vos, M., 2024. Cryopreservation of ovarian tissue for fertility preservation in breast cancer patients: time to stop? Reprod Biomed Online 49,, 103939 PMID: 38733675.

Poulsen, LC, Warzecha, AK, Bülow, NS, Bungum, L, Macklon, NS, Yding Andersen, C, Skouby, SO, 2022. Effects of letrozole cotreatment on endocrinology and follicle development in women undergoing ovarian stimulation in an antagonist protocol. Hum Reprod 37, 1557–1571 PMID: 35652260.

Yasui, T, Hayashi, K, Mizunuma, H, Kubota, T, Aso, T, Matsumura, Y, Lee, JS, Suzuki, S., 2012. Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. Maturitas 72, 249–255 PMID: 22572589.

Received 2 July 2024; received in revised form 16 August 2024; accepted 31 August 2024.