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FERTILITY PRESERVATION

Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice

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Abstract This paper describes the success and expansion of ovarian tissue cryopreservation and transplantation as a fertility restoration procedure, with the largest series of 60 live births worldwide reported. By repeating the procedure, ovarian activity can be restored for more than 11 years.

Keywords Ovarian tissue transplantation · Live births · Fertility preservation · Cancer patients

Introduction

Fertility preservation (FP) in young women will be a major challenge over the next 5 years, in the context of treating cancer or benign diseases or for social reasons [1]. Unfortunately, only small fractions of patients at risk of premature ovarian failure (POF) are referred to fertility preservation specialists to discuss the different options of FP.

Capsule Ovarian tissue transplantation restores ovarian secretion and allow natural conception.

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Mature oocyte cryopreservation

Embryo and mature oocyte cryopreservation are the only methods endorsed by ASRM.

MII oocyte vitrification represents the ideal fertility preservation option in case of benign diseases, social reasons, and even in cancer women if they are post-pubertal and if chemotherapy could be delayed.

Studies of oocyte vitrification in egg donation programs demonstrated very high oocyte survival rates (92.52 %) and ongoing pregnancy rates (as high as 43.7 %) [2]. Nevertheless, patients should be aware that around 20 vitrified oocytes are required to achieve a live birth.

Indeed, in the most experienced teams of the world, the live birth rate per vitrified oocyte is 5–7 % in egg donation program but these results cannot be extrapolated to cancer women.

Ovarian tissue cryopreservation (OTC)

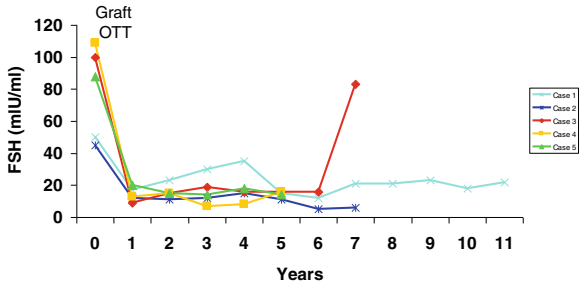
For prepubertal girls and women who cannot delay the start of chemotherapy, OTC is the only FP option available [1, 3].

It has also been demonstrated in some series [1] that OTC during childhood was feasible and safe [1, 4]. Nevertheless, in that case, left oophorectomy should be performed because of the small size of the ovaries.

Otherwise, in adults, 4–5 ovarian cortical biopsies (1 cm L, 0.5 mm W, 1.5 mm T) are usually taken.

There are essentially two techniques of orthotopic reimplantation (that means "in the pelvic cavity") [1]:

1. If at least one ovary is present, pieces of thawed ovarian are either fixed on the decorticated medulla [1] or pushed by a small cortical incision under the cortical capsula [5, 6].



Case 1: second orthotopic transplantation at 5 years (still functioning after 11y)
Case 2: 3 pregnancies and deliveries (still functioning after 7y)
Case 3: second orthotopic transplantation at 2 years; 1 pregnancy (egg donation) and delivery
Case 4: 2 pregnancies and deliveries (still functioning after 5 years)
Case 5: graft still functioning after 5 years

Fig. 1 Data from a series of five women who underwent ovarian tissue cryopreservation before the age of 22 years (median 19 years) and before any kind of chemotherapy. Case 1—second orthotopic transplantation at 5 years (still functioning after 11 years), case 2—three pregnancies and deliveries (still functioning after 7 years), case 3—second orthotopic transplantation at 2 years; 1 pregnancy (egg donation) and delivery, case 4—two pregnancies and deliveries (still functioning after 5 years), and case 5—graft still functioning after 5 years

2. If the ovary is absent, the ovarian pieces could be placed in a peritoneal window [7, 8].

The advantages of orthotopic ovarian tissue reimplantation are the possibility of natural conception (with demonstrated restoration of fertility) and the favorable environment for follicular development (oxygenation, pressure, presence of peritoneal fluid).

Outcomes

1. *Restoration of ovarian activity*

Restoration of ovarian activity was 100 % if primordial follicles are present. In a first series, three cases had no follicles in their grafted tissue and of course no restoration of activity was detected. It highlights the importance of an "intact" follicular density [9].

The mean duration of ovarian function after transplantation is more or less 5 years in case of high follicular density which is age dependent.

Data from a series of five women who underwent ovarian tissue cryopreservation before the age of 22 years (median 19 years) and before any kind of chemotherapy (Fig. 1) demonstrated that the duration of ovarian activity restoration was more than 5 years

Table 1 Series of 60 live births after transplantation of frozen-thawed ovarian cortex

	Cryopreservation procedure	Number of transplanted women desiring pregnancy	Number of live births (..)=ongoing pregnancies
Donnez and Dolmans et al.	SF	19	8 (+1)
Meirow et al.	SF	NA	6
Demeestere et al.	SF	NA	3
Andersen's et al.	SF	25	8
Silber et al.	SF	6	4
Piver et al. and Roux et al.	SF	NA	3 (+1)
Pellicer et al.	SF	33	6[a] (+3)
Revel et al.	SF	NA	2
Dittrich et al.	SF	20	6
Revelli et al.	SF	NA	1
Callejo et al.	SF	NA	1
Stern, Gook, and Rozen	SF	14	3[a]
Kawamura and Suzuki et al.	VF	NA	2
Burmeister and Kovacs, et al.	SF	2	1
Rodriguez-Wallberg and Hovatta et al.	SF	NA	1
Tanbo et al.	SF	2	2
Agarwal et al.[b]	SF	NA	1
Makolkin et al., and Kalugina et al.[b]	SF	NA	2

Adapted from Fertil Steril [9], the Lancet [10], from two correspondences to the Lancet by Rozen et al. [16], by Andersen [11], and from two publications by Rodriguez-Wallberg et al. [17] and by Tanbo [18]

SF slow freezing, *VF* vitrification

[a] Twins

[b] Personal communication

and that by repeating the procedure, ovarian activity can be restored for more than 11 years. These encouraging results on ovarian function restoration now lead us to speculate that in the future, ovarian cortex cryopreservation at a young age, followed by reimplantation at menopause, could be an alternative to hormonal replacement therapy.

2. *Live birth*

So far, 60 live births were reported either in peer reviewed journals or in abstracts of congress (Table 1). All of them but two were obtained when the slow freezing technique was applied.

As the number of transplantations (the denominator) is not known, results for three centers (Denmark, Spain, Belgium) were collected in a large series [9], and 2 years later in the largest series taking into account a fourth center (Germany) [10]. The number of women who conceived is 25 %. Importantly, at least, two women delivered each three babies proving the long-term efficacy of the technique in terms of fertility [10, 11].

Combined technique

(a) OTC might be combined with the removal of small antral follicles (by puncture) including those present in the dissection medium (Fig. 2). The first pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient was recently published by Prasath et al. [12], followed by a second live birth reported by Segers et al. at the Brussels meeting [13].

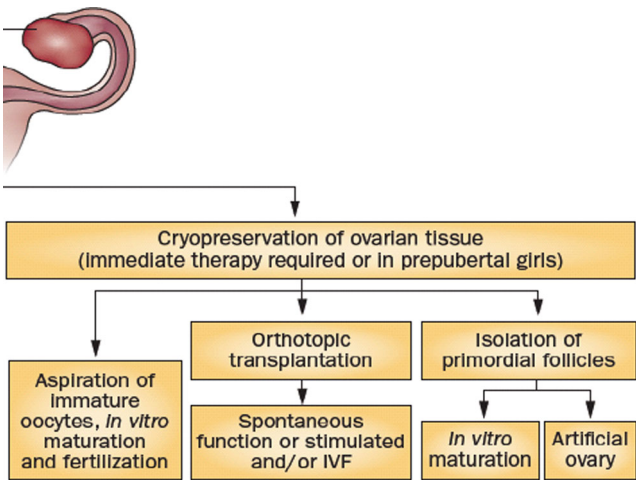


Fig. 2 OTC might be combined with the removal of small antral follicles (by puncture) including those present in the dissection medium. Adapted from Donnez and Dolmans (Nature End Rev)

(b) OTC could be performed between days 0 and 3 of controlled ovarian stimulation (COS) and then, by continuing COS, ovum pick-up with a view of vitrifying oocytes could increase the efficacy of the fertility preservation. It was indeed recently demonstrated that the number of oocytes obtained after COS, following immediately OTC, was similar to a control group of the same age [14].

Conclusion

Only a small fraction of patients at risk of POF is referred to specialists to discuss fertility preservation options; of this group, only a few women actually undergo fertility preservation owing to social, economic, or technical hurdles. In addition, women are increasingly postponing childbearing to later in life for social reasons, and the incidence of most cancers increases with age.

Health-care providers, particularly the oncologists and hematologists, should address the possibility of infertility in patients requiring gonadotoxic drugs and/or irradiation [15].

They should advise them as to available methods of FP, referring them to appropriate reproduction specialists. All patients should receive correct information based on evidence in terms of fertility, and it is time not to consider anymore ovarian tissue cryopreservation and reimplantation as an experimental procedure.

References

1. Donnez J, Dolmans MM. Fertility preservation in women. Nat Rev Endocrinol. 2013;9:735–49.
2. Cobo A, Garcia-Velasco JA, Domingo J, Remohí J, Pellicer A. Is vitrification of oocytes useful for fertility preservation for age-related fertility decline and in cancer patients? Fertil Steril. 2013;99(6):1485–95.
3. Donnez J, Dolmans MM. Ovarian tissue freezing: current status. Curr Opin Obstet Gynecol. 2015;27(3):222–30.
4. Jadoul P, Dolmans MM, Donnez J. Fertility preservation in girls during childhood: is it feasible, efficient and safe and to whom should it be proposed? Hum Reprod Update. 2010;16(6):617–30.
5. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. 2005;353(3):318–21.
6. Andersen CY, Rosendahl M, Byskov AG, Loft A, Ottosen C, Dueholm M, et al. Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod. 2008;23(10):2266–72.
7. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet. 2004;364(9443):1405–10.
8. Donnez J, Jadoul P, Pirard C, Hutchings G, Demylle D, Squifflet J, et al. Live birth after transplantation of frozen-thawed ovarian tissue

after bilateral oophorectomy for benign disease. Fertil Steril. 2012;98(3):720–5.
9. Donnez J, Dolmans MM, Pellicer A, Diaz-Garcia C, Sanchez Serrano M, Schmidt KT, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. Fertil Steril. 2013;99(6): 1503–13.
10. Donnez J, Dolmans MM, Pellicer A, Diaz-Garcia C, Ernst E, Macklon KT, et al. Fertility preservation for age-related fertility decline. Lancet. 2015;385(9967):506–7.
11. Andersen CY. Success and challenges in fertility preservation after ovarian tissue grafting. Lancet. 2015;385(9981):1947–8.
12. Prasath EB, Chan ML, Wong WH, Lim CJ, Tharmalingam MD, Hendricks M, et al. First pregnancy and live birth resulting from cryopreserved embryos obtained from in vitro matured oocytes after oophorectomy in an ovarian cancer patient. Hum Reprod. 2014;29(2):276–8.
13. Segers I, Mateizel I, Guzman L, Romero S, Van Moer E, Smitz J, et al. Congress on "Freezing oocytes embryos and ovarian tissue". Brussels; 2015.
14. Dolmans MM, Marotta ML, Pirard C, Donnez J, Donnez O. Ovarian tissue cryopreservation followed by controlled ovarian stimulation and pick-up of mature oocytes does not impair the number or quality of retrieved oocytes. J Ovarian Res. 2014;7:80.
15. Dolmans MM, Jadoul P, Gilliaux S, Amorim CA, Luyckx V, Squifflet J, et al. A review of 15 years of ovarian tissue bank activities. J Assist Reprod Genet. 2013;30(3):305–14.
16. Rozen G, Agresta F, Gook D, Braat D, Stern CJ. Success and challenges in fertility preservation after ovarian tissue grafting. Lancet. 2015;385(9981):1947.
17. Rodriguez-Wallberg KA, Karlström PO, Rezapour M, Castellanos E, Hreinsson J, Rasmussen C, et al. Full-term newborn after repeated ovarian tissue transplants in a patient treated for Ewing sarcoma by sterilizing pelvic irradiation and chemotherapy. Acta Obstet Gynecol Scand. 2015;94(3):324–8.
18. Tanbo T, Greggains G, Storeng R, Busund B, Langebrekke A, Fedorcsak P. Autotransplantation of cryopreserved ovarian tissue after treatment for malignant disease - the first Norwegian results. Acta Obstet Gynecol Scand. 2015. [Epub ahead of print].