Ovarian cortex transplantation: time to move on from experimental studies to open clinical application

In the context of treating cancer, fertility preservation (FP) in young women is a major challenge. Many questions remain because controversial issues still exist (1). Unfortunately, only a small number of patients at risk of premature ovarian failure are referred to FP specialists to discuss different options (1). As reproduction specialists, we consider it vital to provide oncologists, hematologists, and all healthcare providers with accurate information, based on firm evidence, on fertility-sparing treatments before cancer treatment, which could potentially have devastating consequences on their future quality of life. Our goal is to convince them to refer patients at risk of ovarian failure to FP specialists to discuss the different options.

It is well demonstrated that embryo and mature oocyte cryopreservation, the only methods currently endorsed by the American Society for Reproductive Medicine, are very effective means of preserving fertility in cases of benign disease, social reasons, and even cancer, as long as patients are postpubertal and chemotherapy can be delayed.

However, these methods are not appropriate for everyone. Indeed, for prepubertal girls and women who cannot delay the start of chemotherapy, ovarian tissue cryopreservation (OTC) is the only FP option available. We would therefore like to demonstrate that enough evidence now exists to stop considering OTC an investigational approach.

LIVE BIRTH RATE AFTER OTC AND REIMPLANTATION IN A SERIES OF 111 WOMEN

Many cases of reimplantation of cryopreserved ovarian tissue have been performed throughout the world and, to date, 60 live births have been reported in peer-reviewed journal and abstracts of congresses. All but two of the births were achieved using the slow-freezing technique. With the number of published live births after OTC and reimplantation increasing month after month, the worldwide expansion of this technique suggests its application in routine clinical practice. In this series of 60 reported cases, the number of reimplantations performed in each center is unknown, as well as, sometimes, the intrinsic ovarian activity before grafting. This is the reason why we collected data from centers where information concerning the number of reimplantations and the hormonal status of the patient before grafting was known.

To obtain information on the pregnancy rate per reimplantation based on evidence, results from three centers (Denmark, Spain, Belgium) were collected in a large series (2), with the addition of a fourth center (Germany) 2 years later (3). Since the correspondence of Andersen and Rozen et al. to *The Lancet* (4, 5) we have also added to Table 1, the Australian series data as well as new data from the Danish team.

In this large series numbering 111 cases, the proportion of women who conceived was 29% (n = 32). Because the number of transplantations (the denominator) is known, this information is highly relevant and based on evidence. Two women delivered three babies each, proving the efficacy of the technique, as well as the possibility of conceiving naturally several times after only one procedure (2, 4).

Moreover, OTC might be combined with removal of immature oocytes from small antral follicles present in ovarian cortex or found in the dissection medium. Ovarian tissue cryopreservation could also be associated with mature oocyte vitrification, with OTC performed between days −1 and +3 of controlled ovarian stimulation, followed by oocyte pickup (1). This would then optimize and maximize fertility restoration possibilities.

PROTECTION OF OVARIAN FUNCTION BY GNRH-A: QUESTIONS REMAIN, AS WELL AS CONTROVERSIAL ISSUES

Some studies on the possible advantages of GnRH agonist (GnRH-a) cotreatment during chemotherapy suggest a potential benefit, with increased rates of recovery of menses. Unfortunately, pregnancy rates do not show the same increase. Indeed, we recently reviewed this topic and failed to demonstrate any real benefit of GnRH-a in terms of FP, concluding that its use remains questionable (1). Moreover, according to the 2013 American Society for Reproductive Medicine recommendations, GnRH-a should not be relied on to preserve fertility.

A recent publication led to the conclusion that the ovaries are protected from follicular depletion by coadministration of

TABLE 1

Results from five centers, allowing evaluation of pregnancy and live birth rates, because the number of transplants is known.

Team	Transplanted women	Women who conceived (%)	Women who gave birth	Live births (ongoing pregnancies)	Miscarriages
Donnez and Dolmans' team (2)	19	7	5	8 (+1)[a,b]	1
Andersen's team (4)	25	8	6	8[b]	2
Pellicer's team (2)	33	8	4	6[a,c] (+3)	3
Dittrich's team (3)	20	7	6	8[a]	1
Rozen's team (5)	14	2	2	3[c]	0
Total	111	32 (29)	23	33 (+4)	7

Note: Data from references 2-5. Values are number, except where noted.
[a] One woman delivered twice.
[b] One woman delivered three times.
[c] One twin delivery.

Donnez. Ovarian cortex transplantation. Fertil Steril 2015.

GnRH-a in young women receiving cyclophosphamide (6). Although conducted as a randomized controlled trial, the study contains some weaknesses and limitations (some of them acknowledged by the authors themselves). One of the primary objectives of the study was recovery of menses, which does not equate to restoration of fertility. It is well known that perimenopausal women can still have irregular menses despite being infertile. Although serum antimüllerian hormone and antral follicle count are known to be the best markers of the follicle pool, they were not investigated. In a letter to the *New England Journal of Medicine* concerning Moore et al.'s article (6), Oktay et al. (7) clearly demonstrated an absence of significant difference ($P=.188$) in the pregnancy rate between the two groups when they recalculated the numbers on the basis of patients attempting to conceive, rather than all women in each group.

Despite this recent publication (6), the use of GnRH-a to protect ovarian function during chemotherapy remains questionable and controversial, and there is currently not enough evidence to consider the administration of GnRH-a as a unique approach to preserve fertility during adjuvant chemotherapy. The real benefits in terms of FP should be evaluated in terms of ongoing pregnancies and live births and not only in terms of recovery of menses.

To conclude, in the presence of data increasingly demonstrating the safety and efficacy of OTC, we firmly believe that the procedure should no longer be considered experimental. This technique should be implemented in all cancer centers to prevent the devastating effects of cancer treatment on the female gonads, especially in prepubertal girls or when chemotherapy cannot be delayed.

Jacques Donnez, M.D., Ph.D.[a]
Marie-Madeleine Dolmans, M.D., Ph.D.[b,c]
César Diaz, M.D., Ph.D.[d]
Antonio Pellicer, M.D., Ph.D.[d,e]

[a] Société de Recherche pour l'Infertilité, Brussels, Belgium; [b] Pôle de Gynécologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels; [c] Gynecology Department, Cliniques Universitaires St. Luc, Brussels, Belgium; [d] Hospital Universitario La Fe, Valencia, Spain; and [e] Instituto Valenciano de Infertilidad, Valencia, Spain

http://dx.doi.org/10.1016/j.fertnstert.2015.08.005

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