Egg Freezing in Childhood and Young Adult Cancer Survivors

Francesca Filippi, MD,[a] Cristina Meazza, MD,[b] Alessio Paffoni, MSc,[a] Francesco Raspagliesi, MD,[b] Monica Terenziani, MD,[b] Edgardo Somigliana, MD, PhD[a]

abstract

Fertility preservation in prepubertal and young adolescent girls scheduled for chemotherapy is a demanding situation. Despite the recent impressive improvements of ovarian cortex cryopreservation, significant limitations persist. The technique remains experimental, it exposes the girl to the risks of surgery and to an iatrogenic insult to the ovarian reserve, and there is no guarantee of use because not all girls will undergo re-implantation. Moreover, it is impossible to respect all the requested conditions for a valid informed consent. The girl is minor, the time for decision is very short, and the prospect of not surviving clouds both the girl and her relatives. An alternative but neglected option is oocyte cryopreservation after the end of cancer treatments, when the girl reaches adulthood. This possibility can overcome some of the limitations of ovarian cortex freezing and may be considered for girls scheduled for a chemotherapy at low or medium risk of ovarian reserve impairment. In this case report, we describe the case of a young female patient with cancer who survived 2 chemotherapies for 2 distinct cancers and who was diagnosed with reduced ovarian reserve. The patient underwent 3 cycles of ovarian hyperstimulation and ultimately stored 19 oocytes. The success obtained in this girl suggests consideration of egg freezing as an alternative fertility-preservation procedure in prepubertal and young adolescent girls scheduled for chemotherapy. However, cryopreservation of ovarian tissue remains the only option for those scheduled for chemotherapies at high risk of ovarian reserve impairment.

Fertility preservation in women with malignancies has received growing interest during the past 2 decades and there is now a general consensus that these women should systematically receive comprehensive counseling before starting treatments and, if possible, they should be offered the possibility to bank oocytes or ovarian cortex.[1–3]

Despite the outstanding progresses of oncofertility in recent years, prepubertal and young adolescent girls with cancer still represent a demanding condition. The only available option at the time of diagnosis is surgical excision and freezing of an ovarian cortex fragment. To date, only 1 live birth has been reported in the literature with the use of tissue obtained during childhood.[4] Even if pregnancies with the use of frozen ovarian tissue from adult women have been repeatedly reported worldwide,[5] the technique remains experimental because the overall total number of live births is relatively low and the effectiveness and safety of the technique in everyday clinical practice is still uncertain. However, despite these concerns, ovarian cortex freezing is highly recommended in girls who are scheduled for chemotherapy at high risk of complete

[a]*Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; and* [b]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

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Address correspondence to Alessio Paffoni, Fondazione Ca' Granda, Ospedale Maggiore Policlinico - Infertility Unit, Via Fanti 6 – 20122, Milano, Italy. E-mail: alessio.paffoni@policlinico.mi.it

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depletion of the ovarian reserve after the end of treatments.

Interestingly, Mertes[6] recently questioned the dogma that ovarian cortex biopsy should be considered the only option in prepubertal and young adolescent girls. In girls scheduled for a chemotherapy at low or medium risk of ovarian function impairment, she advocates the alternative option of freezing oocytes after the end of treatments when they reach adulthood. In fact, these girls are likely to be fertile after treatment but face the risk of premature exhaustion of the ovarian reserve.[7,8] The concerns are mostly ethical. Ovarian cortex biopsy is experimental, requires surgery, inevitably adds relevant stress to the girl and her relatives, and a consistent (albeit poorly defined) proportion of girls will actually never use the banked tissue and thus would be uselessly exposed to surgical risks and to iatrogenic damage to the ovarian reserve. Moreover, Mertes[6] points out that the informed consent for the procedure has weak and arguable bases considering that it is given in a very stressful context and, most importantly, is obtained by the relatives and not directly by the patient because she is a minor.

Despite these sound considerations, the possibility of freezing eggs in childhood cancer survivors when they reach adulthood has received scant attention. Some studies report on ovarian responsiveness or in vitro fertilization outcome in women previously exposed to chemotherapy,[9–14] but specific data on postchemotherapy oocyte freezing in childhood survivors is lacking. Of relevance here is that ovarian reserve may be compromised after treatments and this may hamper the effectiveness of the procedure. To support the practicability of this option, we herein report on a young woman who survived 2 cancers and who attempted to freeze her oocytes at 22 years of age.

CASE REPORT

R.G. was born in 1992 and she was diagnosed with Hodgkin lymphoma (stage IIIsA) at the age of 13 years (2005). She was successfully treated with mediastinal radiotherapy (dose 25 Gy) and chemotherapy according to an ABVD regimen for 6 cycles (cumulative doses: doxorubicin 300 mg/m^2, bleomycin 120 mg/m^2, vinblastine 72 mg/m^2, dacarbazine 4500 mg/m^2). In 2013, at age 21, she was diagnosed with synovial sarcoma of the left lung, adjacent to the radiation field. The lesion was surgically removed. Additionally, she received 6 cycles of ifosfamide. The total cumulative dose was 84 mg/m^2. Since then, she is disease-free. The girl and her relatives were not counseled about the possibility of fertility preservation at the time of first diagnosis (no option was available in 2005). At the time of second diagnosis (2013), oocyte cryopreservation before start chemotherapy could be considered, but the girl was upset by the clinical situation and resolutely declined specific counseling and any treatment. She completed chemotherapy in June 2013.

In June 2014, at age 22, the woman was evaluated in the Fertility Preservation service of the Istituto Nazionale dei Tumori. She reported regular but short menstrual cycles (mean duration of 24 days) and the biomarkers of ovarian reserve were suggestive of reduced but not compromised ovarian reserve. Specifically, day 3 serum follicle-stimulating hormone (FSH) was 7.6 IU/mL, serum anti-Müllerian hormone (AMH) was 0.9 ng/mL, and total antral follicle count (AFC) was 7. BMI was 28 kg/m^2. She was counseled about the reproductive significance of her clinical history. Because she was not in the social and financial condition to plan for a natural pregnancy in the short term, it was decided to perform oocyte freezing. Three cycles of ovarian hyperstimulation were performed during a 10-month period in our Infertility Unit. The details of these cycles are illustrated in Table 1. Oocytes were frozen by using the vitrification technique as described elsewhere.[15] Overall, 16 metaphase-II and 3 metaphase-I oocytes were frozen. The costs of the procedures (including 6 years of maintenance in the biobank at a cost of € 100 per year) were € 12 330. The mean costs per frozen oocyte and per metaphase-II frozen oocyte were € 649 and € 771, respectively. The procedure was mainly supported by the public health system with the exception of the maintenance in the biobank and the costs of the gonadotropin-releasing hormone (GnRH) analogs that were supported by the patient (corresponding to a total of € 1538). The woman gave her informed consent for the use of her data for research purposes.

DISCUSSION

This case report illustrates a case of a young woman who did not undergo fertility preservation at the time of the diagnoses of cancer but who was subsequently able to freeze 19 oocytes, of whom 16 were metaphase-II despite a significant impairment of the ovarian reserve. Based on previous data on the effectiveness of egg freezing (4.5%–12.0% per warmed oocyte)[17–19] and considering the 16 metaphase-II oocytes, this would lead to a 52% to 87% chance of pregnancy. This case strengthens the importance of counseling all childhood cancer survivors when they reach adulthood and to consider egg freezing. Albeit neglected in the literature,[19] we agree with previous authors who advocated childhood cancer survivors as a new important indication for the procedure.[6,20] Noteworthy, oocyte freezing once reaching adulthood is not incompatible with procedures performed at the time of cancer

TABLE 1 Characteristics of the 3 Hyperstimulation Cycles

Characteristics	1st Cycle	2nd Cycle	3rd Cycle
Period	January 2015	May 2015	October 2015
Protocol of hyperstimulation	GnRH antagonists	GnRH antagonists	GnRH antagonists
Duration of stimulation, d	12	10	10
Drug used			
Corrifollitropin 150 μg, ampules	1	1	1
Recombinant FSH, IU	2850	2700	2100
GnRH antagonists, ampules	4	5	4
Trigger	hCG 10 000 IU	hCG 10 000 IU	Triptorelin 0.2 mg
No. of follicles at the time of trigger			
Diameter >15 mm	7	5	8
Diameter 11–15	2	3	4
No. oocytes retrieved	9	6	8
No. of metaphase-II oocytes	4	5	7
No. of metaphase-I oocytes	3	0	0
Total no. of oocytes frozen	7	5	7
Clinical complications	None	None	None
Costs			
Drugs	€ 1834	€ 1620	€ 1580
Procedure	€ 2232	€ 2232	€ 2232
Total	€ 4066	€ 3852	€ 3812

The costs of the pharmacological compounds were obtained through the Web site of the official Italian Institute for Drugs (http://www.agenziafarmaco.gov.it) and adapted to a discount obtained for some of these drugs (corrifollitropin and recombinant FSH) by the local authorities (http://www.aslmi1.mi.it/). The cost of the oocyte retrieval was derived from the regional drug-related group costs (Bollettino Ufficiale Regione Lombardia[16]). The direct and indirect costs supported by the women for referrals were excluded. hCG, human chorionic gonadotropin.

diagnosis, such as ovarian cortex freezing.

Evidence from this case report is obviously insufficient to draw precise clinical indication for an a priori decision to postpone oocyte freezing after the end of treatment. However, we agree with Mertes [6] who suggests discussing this possibility at the time of cancer diagnosis with the affected girl and her relatives, at least in patients who will be exposed to oncologic treatments at low or medium risk of ovarian impairment. In fact, if chemotherapy-related gonadotoxicity is exclusively a quantitative damage, ovarian reserve in survivors may still consent to retrieve good-quality oocytes when these girls reach young adulthood.[21] Interestingly, Thomas-Teinturier et al[22] recently reported that serum AMH and AFC are lower in childhood survivors but still valuable in terms of oocyte cryopreservation. The median age of the studied cohort was 25 years and the median values of AMH and AFC were 1.5 ng/mL and 12.0, respectively. More in general, chemotherapy may cause a significant drop in ovarian reserve that would ultimately lead to a significant reduction in the duration of the fertile period but also concomitantly lets a window of fertility in young adulthood that can be used for egg banking (Fig 1). In this sense, our case report is particularly enlightening because it shows that this option could be valid also in a young woman who had 2 different chemotherapies for 2 distinct cancers. Presumably, the procedure would have been more fruitful if she was treated only for 1 of the 2 tumors.

Costs of the procedure were not unremarkable. In a pure private setting not supported by insurances or public health system, the costs recorded in our case (€ 12 330) would be prohibitive for the vast majority of young women. Moreover, from a public health perspective, the intervention warrants cost-benefit analyses before systematically recommending its routine use. Noteworthy, from an economical point of view, a postcancer approach to fertility preservation has the advantage of excluding from the program women who do not survive cancer, those who are interested in achieving parenthood early, and those whose ovarian reserve appears intact once they reach adulthood. Moreover, this approach has some indisputable advantages from an ethical perspective. The girl and her relatives are not exposed to an additional stress at the time of cancer diagnosis, and the affected patient can give informed consent on her own and in a less stressful and more equilibrated situation. On the other hand, it has to be pointed out that survivors of childhood cancer are frequently lost to long-term follow-up[24] and may not refer for fertility preservation counseling once they reach adulthood. Even if postcancer oocyte banking will be definitely proven to be an effective option in future studies, the high rate of survivors lost to follow-up may significantly affect the ultimate proportion of women achieving parenthood. Moreover, considering drawbacks, it has to be recognized that egg banking is not highly effective and, in some circumstances, this intervention may compare unfavorably with ovarian cortex freezing. Indeed, most

young people want to have at least 2 children,[25] and one may assume that cancer survivors do not differ from the general population. Even if egg banking offers a reasonable chance of pregnancy, its effectiveness inevitably drops when aiming at >1 child. Ovarian cortex freezing might be superior in this regard.

Two main points remain to be clarified. First, predicting the impact of chemotherapy on ovarian reserve is currently challenging.[22] A reliable prediction of chemotherapy-related damage to the ovarian reserve is an indispensable prerequisite to confidently propose postchemotherapy egg banking at the time of cancer diagnosis. This issue is complicated by the possibility that a subgroup of affected girls would not respond to first-line treatment and may thus require second-line (and more harmful) chemotherapy. In this regard, it has to be underlined that one may still successfully perform ovarian cortex biopsies after failure of first-line treatments, in particular in younger girls.[26] Second, even if it is generally accepted that egg freezing is not experimental, definite data on its effectiveness and safety are missing.[17] Data on donors or infertile women are reassuring,[17–19] but this has to be confirmed in independent nonreferral centers. Moreover, we urgently need specific data on the quality of oocytes banked from young women who were previously exposed to gonadotoxic treatments. In our case, >1 year passed between the end of the last chemotherapy and the first freezing cycle (from June 2013 to January 2015). This time period is much longer than the duration of an entire cycle of folliculogenesis,[27] and we could thus exclude exposure of the collected oocytes to chemotherapeutic agents during their growth and maturation. Interestingly, recent evidence failed to document an increased risk of congenital anomalies among female cancer survivors' natural offspring.[28]

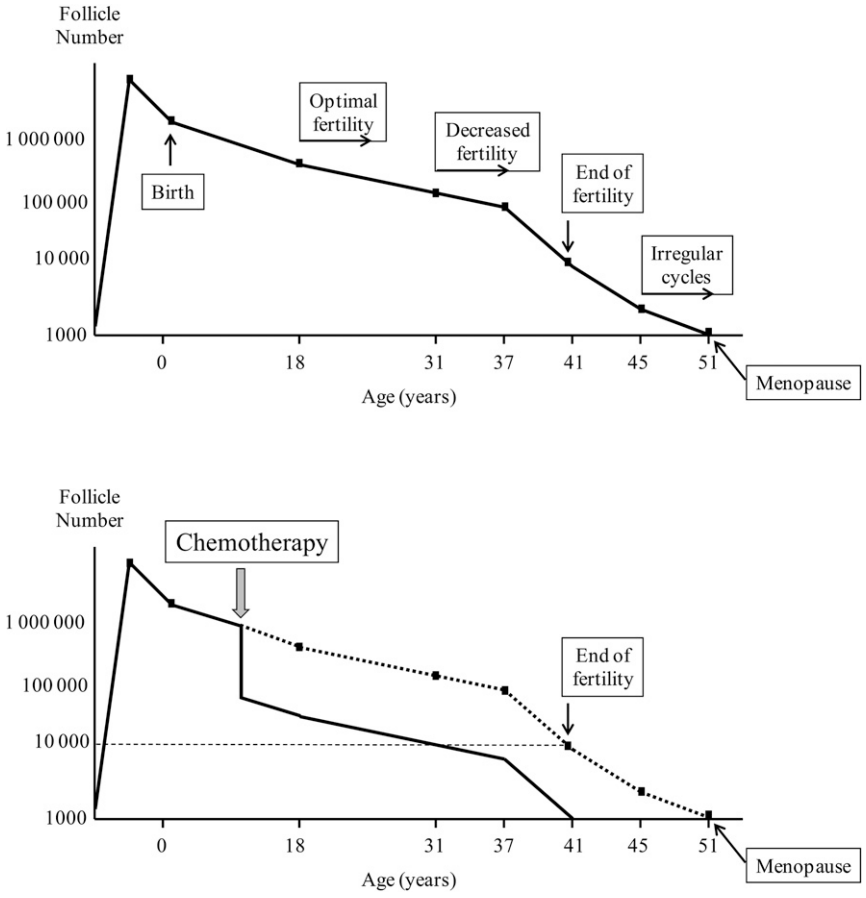

FIGURE 1

Oocyte cryopreservation in childhood cancer survivors: simplified theoretical model. The physiologic reduction in the ovarian reserve and its clinical impact is depicted in the upper panel.[23] The lower panel illustrates the impact of chemotherapy. A relevant drop in ovarian reserve occurs at the time of treatment. Subsequently, the ovarian reserve continues to physiologically decrease. Menopause and the end of the fertile period will occur earlier. This situation, however, consents to take advantage of a window of time in young adulthood to store oocytes. (Adapted and reprinted with permission from te Velde ER, Scheffer GJ, Dorland M, Broekmans FJ, Fauser BCJM. Developmental and endocrine aspects of normal ovarian againg. *Mol Cell Endocrinol*. 1998:145(1-2):68.)

Moreover, emerging evidence on the safety of oocyte cryopreservation for nononcological indications is reassuring.[29]

CONCLUSION

Egg freezing in childhood cancer survivors with reduced (but not depleted) ovarian reserve is possible. However, affected women have to undergo several cycles of hyperstimulation to store a significant number of oocytes. Therefore, even if ovarian cortex freezing should always be considered at the time of cancer diagnosis, omitting the alternative of postcancer oocyte freezing is questionable, at least in girls scheduled for treatment at low or medium risk of ovarian reserve impairment. Further studies are warranted to define the indications, the effectiveness, the cost-effectiveness, and the safety of this approach.

ABBREVIATIONS

AFC: antral follicle count
AMH: anti-Müllerian hormone
FSH: follicle-stimulating hormone
GnRH: gonadotropin-releasing hormone

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