Female fertility preservation: why it does not always mean preservation of fertility

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ABSTRACT

The risk of cancer-related infertility is high for some diseases, but still unclear for others. Due to numerous confounding factors, it is difficult to clarify the impact of cancer itself on female fertility. Oocyte and ovarian tissue cryopreservation offer many cancer patients an opportunity to achieve genetic parenthood, but the real efficacy of the method in terms of live births is still unknown. Since not all women with cancer are at risk of infertility, a customized approach, taking into account the type of disease and therapy, is required in order to optimize female fertility preservation method choice, efficacy and cost-effectiveness. This mini-review focuses on the efficacy of female fertility preservation by oocyte and ovarian tissue cryopreservation, in order to provide some useful tips for oncofertility counseling.

KEYWORDS

Female fertility, fertility preservation, vitrification, oocytes, male breast cancer, fertility preservation efficacy, ovarian tissue.

Introduction

Every year, nearly 5000 Italian women of reproductive age get a cancer diagnosis. Breast, thyroid, cervical, and colon-rectal cancers and melanoma are the most frequently diagnosed types [1]. Cancer itself and the related treatments can affect ovarian function leading to an irreversible worsening of oogenesis, although this scenario is observed only in some patients, depending on their age, the site and stage of the disease, the treatment duration and regimen, the pre-treatment ovarian reserve, and the individual susceptibility. Since not all women with cancer are at risk of infertility, a customized approach, taking into account the type of disease and therapy, is required in order to optimize female fertility preservation method choice, efficacy and cost-effectiveness. More importantly, a realistic assessment of reproductive chances after fertility preservation should be provided during fertility preservation counseling in order to avoid false hopes.

Cancer and infertility

Understanding the role of cancer in infertility is very challenging because of several confounding factors. First, the parameter most frequently used to evaluate ovarian function in cancer patients is the number of oocytes collected after ovarian stimulation, an analysis that should be restricted to young and fertile cancer patients undergoing fertility preservation. Moreover, cancer shares several predisposing factors with infertility, namely a higher body mass index, smoking, lack of physical exercise, poor diet, alcohol consumption and stress [2], and this makes it almost impossible to understand whether infertility is due to these factors, cancer, or both. However, a series of studies

Article history
Received 12 Jul 2023 – Accepted 14 Mar 2024

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reviewed by Friedler *et al*. in 2012 seems to suggest a worsening of ovarian response in cancer patients versus controls, even though the analysis was probably affected by several biases, in particular, the lower gonadotropin administration in the cancer group [3]. Conversely, more recent data show that the presence of cancer itself does not seem to be an independent factor of impaired ovarian response during stimulation [4-11], even though more specific analyses suggest that ovarian cancer and/or high-stage/grade disease could significantly affect ovarian function in terms of collected oocytes [6,9,10,12]. Papers examining the correlation between cancer and ovarian response are listed in Table 1.

A correlation between infertility and cancer treatment is not always documented. The impact of chemotherapy and radiotherapy on ovarian activity depends on the duration of treatment, the drug/irradiation dosages, and the class of drug used. In fact, since regimens such as cyclophosphamide/methotrexate/fluorouracil (CMF), cyclophosphamide/doxorubicin/fluorouracil (CAF), and cyclophosphamide/epirubicin/fluorouracil (CEF) seem to be related to a high risk of amenorrhea (> 80%), other treatments such as doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD), cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) and methotrexate, do not show this correlation. Similarly, infertility after radiotherapy has been described only for some irradiation regimens [1].

Finally, the main factor influencing cancer-related infertil-

Table 1 Papers correlating cancer and ovarian response after stimulation for oocyte freezing.

REFERENCES	OVARIAN RESPONSE WORSENING	NOTES
Pot, 1998	Yes	Included in Friedler, 2012
Oktay, 2006	Yes	Included in Friedler, 2012
Knopman, 2009	Yes	Included in Friedler, 2012
Klock, 2010	Yes	Included in Friedler, 2012
Quintero, 2010	Yes	Included in Friedler, 2012
Michaan, 2010	Yes	Included in Friedler, 2012
Robertson, 2011	Yes	Included in Friedler, 2012
Cardozo, 2015	No	
Quinn, 2017	No	
Tsampras and Roberts, 2017	No	Except for ovarian cancer
Cobo, 2018	No	
Lefebvre, 2018	No	
Dolinko, 2018	No	Except for diffuse diseases
Von Wolff, 2018	No	Except for ovarian cancer
Moraes, 2019	No	
Volodarky-Perel, 2019	Yes	Only in high stage/ grade disease

ity risk is the patient's age. For instance, CMF, CAF and CEF are associated with a high risk of amenorrhea in women older than 40, but no effect on ovarian function is documented in patients under 30 years old. Radiotherapy-related infertility risk is also associated with the patient's age: 5-6 Gy irradiations could lead to infertility in women older than 40, whereas it takes > 30 Gy to result in permanent infertility in younger patients (under 26 years old).

Female fertility preservation strategies

Strategies for female fertility preservation are listed in Table 2.

Embryo freezing

Embryo freezing was the first technique to become established for this purpose, but it is rarely used because of the need for a male partner, and also because of the ethical issues involved. Vitrification at the blastocyst stage is suggested, allowing a more than 90% survival rate, and pregnancy and live birth rates similar to those obtained with replacement of fresh embryos.

Oocyte freezing

Oocyte freezing is the first choice for fertility preservation in post-pubertal women. The slow-freeze technique has been

Table 2 Papers correlating cancer and ovarian response after stimulation for oocyte freezing.

TECHNIQUE	CHARACTERISTICS	NOTES
Embryo freezing	– Male partner, ovarian stimulation and IVF required – Safe – Effective in terms of biological and clinical outcomes – Documented efficacy in fertility preservation	Established
Oocyte vitrification	– Ovarian stimulation and IVF required – No male partner required – Safe – Effective in terms of biological outcomes – Efficacy in fertility preservation still debated	Established
Ovarian tissue cryopreservation	– No ovarian stimulation, IVF or male partner required – Useful in pre-pubertal girls – Safety not fully documented – Invasive – Effective in terms of ovarian function and menstrual cycle resumption – Efficacy in fertility preservation still debated	Open clinical application
Ovarian suppression with LHRH analog	– No ovarian stimulation, IVF or male partner required – Safe – Effective in terms of ovarian function and menstrual cycle resumption – Efficacy in fertility preservation documented in breast cancer patients	Established for patients with breast cancer
Ovarian transposition	– No ovarian stimulation, IVF or male partner required Risk of ovarian cyst formation – Invasive – Effective in terms of ovarian function and menstrual cycle resumption – Efficacy in fertility preservation still debated	Established
In vitro maturation	– Ovarian stimulation and IVF required – No male partner required – Useful in pre-pubertal girls – Safe – Effective in terms of biological outcomes – Efficacy in fertility preservation still debated	Experimental

replaced by vitrification, allowing an almost 90% oocyte survival rate and an 80% fertilization rate. The necessary ovarian stimulation is safe, since no impact on cancer prognosis has been demonstrated, even in patients affected by estrogen receptor-positive breast cancer [13]. Moreover, several strategies are available that allow collection of a higher number of oocytes in a short time, avoiding a significant delay in the cancer treatment [14,15]. Oocyte freezing by vitrification is established and strongly recommended for all post-pubertal patients of reproductive age before cancer treatments [16].

Ovarian tissue cryopreservation

Ovarian tissue cryopreservation is a useful strategy to restore endocrine function in women with cancer who have a high risk of premature ovarian failure due to gonadotoxic cancer treatments, and it is the only choice in pre-pubertal patients [17]. Briefly, small strips of ovarian cortex are removed by laparoscopy and cryopreserved by slow freezing [18]. Ovarian tissue can be collected at any stage of the menstrual cycle and does not require ovarian stimulation, which means that the procedure does not delay cancer treatment. Age and ovarian reserve, the latter shown by anti-Müllerian hormone (AMH) level and antral follicle count (AFC), are the most important patient selection criteria [19]. After thawing, strips are analyzed to exclude the presence of cancer cells, and an orthotopic transplantation is performed on residual ovary or in the pelvic peritoneum. Heterotopic transplantation into pockets created in the subcutaneous space of the abdominal wall, with the aim of obtaining endocrine recovery, has also been reported [20].

LHRH analog administration

The role of luteinizing hormone-releasing hormone (LHRH) analog administration in fertility preservation has been extensively investigated. It could reduce the gonadotoxic effect of cancer treatment in several ways, for example by suppressing FSH secretion and follicular recruitment, activating LHRH ovarian receptors, and, finally, reducing uterine and ovarian perfusion. Many studies have assessed the effect of LHRH analog therapy in breast cancer patients, and several meta-analyses have been published, albeit without consistent conclusions. Conversely, a more recent meta-analysis including five randomized studies, suggests a significant effect of LHRH analog administration, both on menstrual cycle recovery and on pregnancy rate in breast cancer patients with respect to controls [21]. LHRH analog administration is therefore considered an efficient fertility preservation strategy in breast cancer.

Ovarian transposition

Ovarian transposition is the removal of ovaries from the irradiation field. A laparoscopic intervention is required and the efficacy in terms of fertility preservation is still debated. Possible reported risks are the formation of ovarian cysts, as well as difficulty in ovarian metastasis visualization.

Oocyte *in vitro* maturation

Oocyte *in vitro* maturation involves the collection of germinal vesicle-stage oocytes, either without ovarian stimulation, or following short ovarian stimulation and triggering. Oocytes are incubated in specific media to reach the MII stage and vitrified; the main advantage of this method is its rapidity.

The competence of *in vitro* matured oocytes is still an open question, and few data have been published about the efficacy of this technique in terms of live birth rates in oncological settings. For these reasons, *in vitro* maturation is not widespread as a fertility strategy itself, although it could be useful after *ex vivo* oocyte collection in association with ovarian tissue cryopreservation [22].

Efficacy of female fertility preservation

The efficacy of fertility preservation is measured as the patient's chance of achieving one live, healthy baby after cancer treatment. Among the female fertility preservation techniques listed in Table 2, only oocyte vitrification and ovarian tissue cryopreservation are routinely used [19-23].

As regards the efficacy of oocyte vitrification, high survival and fertilization rates are reported, but these outcomes do not reflect the goal of fertility preservation. In fact, the clinical efficacy of female fertility preservation is reflected in the live birth rate per frozen oocyte. Unfortunately, this is difficult to estimate as the rate of oncological patients seeking pregnancy with their oocytes frozen prior to the cancer treatment is less than 8% (Table 3), and this is directly reflected in the low number of babies obtained in this specific patient group (Table 4).

Another key point is that oocyte vitrification is a less efficient technique, since many oocytes are needed to get a baby. The number of oocytes required is strongly associated with the patient's age: for instance, in women < 35 years old, at least 8 oocytes are needed to obtain a cumulative live birth rate of about 35%, whereas the same number of oocytes in women > 35 years old seems to provide a cumulative live birth rate of

Table 3 Patients seeking oocyte thawing according to the reason for cryopreservation.

REFERENCES	PATIENTS SEEKING OOCYTE THAWING (%)	OOCYTE FREEZING REASON
Hodes-Werts, 2013	6%	Non-oncological
Garcia-Velasco, 2013	1.2%	Oncological
Martinez, 2014	2.9%	Oncological
Alvarez, 2018	2%	Oncological
Balkenende, 2018	7%	Both oncological and non-oncological
Cobo, 2018	7.5%	Oncological
Cobo, 2018	12.2%	Non-oncological
Diaz-Garcia, 2018	4.8%	Oncological
Specchia, 2019	4.5%	Oncological

about 29%. More recent data seem to confirm this, describing a live birth rate of about 40% with at least 10 frozen oocytes in patients < 35 years old [7,11]. Taken together, the literature data suggest that no fewer than 8-15 mature oocytes should be banked to provide a realistic chance of motherhood in cancer patients [7,11,23], and this estimate is confirmed by a recent Italian paper where the mean number of stored oocytes in oncological patients was 9.5±6.1 [24].

Regarding the efficacy of ovarian tissue cryopresevation, recently published data suggest that this technique could provide endocrine recovery in more than 60% of patients, a clinical pregnancy in 58% of patients, and a live birth rate of about 18–30%. Moreover, more than 130 live births have been reported [25-27]. Importantly, since natural conception has been reported in 60% of transplanted patients, pregnancy and live-birth rates in patients submitted to IVF seem to be significantly lower than in the general IVF population, corresponding to patients with poor ovarian reserve [28]. Recently, many authors have suggested that ovarian tissue cryopreservation fulfills the criteria for an established method rather than an experimental one [29], and in some centers the ovarian tissue cryopreservation is formally considered an "open clinical application" procedure [30]. Nevertheless, there is a need for more data about the efficacy in pre-pubertal patients and the safety of transplantation, and for an ovarian tissue cryopreservation world registry to definitively remove the experimental label from this fertility preservation technique. Moreover, the real efficacy of ovarian tissue cryopreservation is not known because of the low number of surgical operations aimed at preserving ovarian tissue and the low number of transplants performed.

Discussion

The main conclusions of this mini-review are listed in Box 1.

Table 4 Babies born from oocytes cryopreserved for oncological reasons

REFERENCES	TECHNIQUE	STORED OOCYTES (N°)	LIVE BIRTHS (N°)	GESTATIONAL AGE (WEEKS)	BIRTH WEIGHT	REPORTED CONGENITAL DISEASES
Yang, 2007	SF	13	1	37	3062	No
Porcu, 2008	SF	7	2	38	2100 2400	No No
Sanchez-Serrano, 2010	Vit	16	2	34	1650 1830	No No
Kim, 2011	Vit	7	1	35	2410	No
Garcia-Velasco, 2013	Vit	4	1	39	3440	No
Alvarez, 2014	Vit	14	1	38	2650	No
Martinez, 2014	Vit	4 5 3 8	1 1 1 1	40 40 40 38	3440 2850 3220 2920	No No No No
Alvez Da Motta, 2014	Vit	28	1	At term	2970	No
Doyle, 2016	Vit	N.R.	1	N.R.	N.R.	No
Druckenmiller, 2016	SF/Vit	N.R.	2 1 1 1	33 40.8 38.6 39	2087 1452 2858 3357 3311	No No No No No
Perrin, 2016	Vit	5	1	37.5	3180	No
Specchia, 2019	Vit	6.5±3.5*	1 1	41 38	3720 2660	No No

Data expressed as mean ± standard deviation. **SF**: slow freeze; **Vit**: vitrification; **NR**: not reported

Box 1

FEMALE FERTILITY PRESERVATION – MAIN CONCLUSIONS
Literature data, while not definitive, do not seem to support a generic effect of cancer on ovarian function
Ovarian cancer and high stage/grade disease could reduce the ovarian function
More data are needed to improve the efficacy of female fertility preservation by oocyte and ovarian tissue cryopreservation
More appropriate terminology should be adopted during counseling, in order to avoid generating false hopes

The first choice for female fertility preservation is oocyte vitrification. Several reports confirm that ovarian stimulation in cancer patients is safe, since no significant worsening of oncological prognosis has been proven in patients submitted to fertility preservation compared with controls. The safety of pregnancy has also been documented — indeed, relapses have not been found to be significantly increased in patients becoming pregnant after cancer. Nevertheless, less than half of young oncological patients are informed about the possibility of banking oocytes prior to cancer treatment, no more than 8% of oncological patients seek pregnancy with oocytes, and to date few babies have been born in this population. Cultural, social and economic factors are responsible for the low rate of possible candidates for fertility preservation who receive specific counseling, whereas the low utilization rate of oocytes could be associated with other reasons, such as recovery of ovarian function (observed especially in young patients), patients choosing to delay starting a family or deciding not to have children (due to the risk of oncogenetic transmission) and, finally, patient death. Again, in some cases more than 10 years may elapse prior to oocyte thawing, due to the young age at the time of freezing or to the prolonged duration of cancer treatment (in the case of estrogen receptor-positive breast cancer). Some open questions remain about the use of vitrification in the oncological setting: the most important issue is the lack of a long-term follow up of babies conceived from vitrified oocytes, and the effect of high concentrations of cryoprotectant agents on oocyte competence; the most effective vitrification tools and freezing/warming protocols are also debated. For all these reasons, it is not possible clarify the real efficacy of female fertility preservation by oocyte vitrification.

When oocyte freezing is not feasible, ovarian tissue cryopreservation could be considered. The first successes with ovarian tissue cryopreservation, dating back to 2004, generated considerable confidence and optimism around this technique. However, ovarian tissue cryopreservation is still not established and many difficulties prevent its standardized application. Since a great advantage of ovarian tissue cryopreservation is its capacity to restore endocrine function, it could be offered as an alternative to non-experimental techniques, very useful in the case of young women at high risk of premature ovarian failure due to sterilizing high-dose chemotherapy.

Importantly, as suggested by several authors, the efficacy of ovarian tissue cryopreservation seems to depend strongly on patient selection [19,27].

Conclusions

Oocyte vitrification and ovarian tissue cryopreservation are routinely used as fertility preservation strategies, even though their real efficacy can be only estimated. Data reported in this mini-review lead us to deduce that fertility preservation does not always mean preservation of fertility. In our opinion, this should be reflected in the fertility preservation counseling and decision-making process; in short, we agree with Grynberg and Sermondade, who suggest that the terminology used should be reconsidered in order to avoid generating false hopes about future motherhood [31]. During counseling the term "fertility preservation" should be replaced with a more appropriate one such as "gamete preservation", "oocyte banking", or "gonadic tissue banking" in order to clearly express the concept that storing biological samples of reproductive cells does not always mean that fertility will be preserved. Evidence-based medicine can provide clear information about the real chances of conceiving after cancer. This evidence should help doctors to provide more correct information, which in turn would prevent patients from harboring false hopes about their chances of having a child.

Finally, better follow up after cancer treatment could help patients to decide whether to use or dispose of their banked oocytes.

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