

Fertility issues in young breast cancer patients: what women want

Matteo Lambertini¹, Ana Catarina Pinto², Lucia Del Mastro³

¹Department of Medical Oncology, U.O. Oncologia Medica 2, IRCCS AOU San Martino-IST, Genova, Italy; ²Breast Data Centre and Medicine Department, Medical Oncology Unit, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium; ³Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, IRCCS AOU San Martino-IST, Genova, Italy

Correspondence to: Matteo Lambertini. U.O. Oncologia Medica 2, IRCCS AOU San Martino-IST, Largo Rosanna Benzi 10, Genova 16132, Italy. Email: matteo.lambertini@hsanmartino.it.

Submitted May 20, 2014. Accepted for publication May 22, 2014.

doi: 10.3978/j.issn.2072-1439.2014.06.12

View this article at: <http://dx.doi.org/10.3978/j.issn.2072-1439.2014.06.12>

Breast cancer is the most common tumor type in young women of reproductive age: approximately 7% of breast cancer cases are diagnosed in women ≤ 40 years and this corresponds to more than 40% of all malignancies diagnosed in this age group (1).

The available anticancer treatments (surgery, radiotherapy, chemotherapy, endocrine therapy and biologic therapy) have improved both disease-free survival (DFS) and overall survival (OS) in young early breast cancer patients but they can cause acute and chronic side effects, such as a negative impact on gonadal function that may lead to impaired fertility (2). The fertility issues in these patients have acquired a growing importance in the last few years not only because of the improved prognosis of cancer patients but also due to the tendency of delaying child-bearing in western countries, so that many women can be childless or may want to enlarge their family at the time of breast cancer diagnosis (3). A new medical discipline, named “oncofertility” (a product of the crosstalk between oncology and reproductive medicine) has emerged in recent years: it is a new concept that describes an exciting integrated network of clinical resources with the goal to develop methods to spare or restore reproductive function in young cancer patients (4).

There are four main available strategies, standard and experimental, for fertility preservation in young early breast cancer patients: embryo cryopreservation, cryopreservation of oocytes, cryopreservation of ovarian tissue and temporary ovarian suppression with luteinizing hormone-releasing hormone analogues (LHRHa).

To date, cryopreservation of embryos and of mature oocytes are the only techniques that are considered standard

by the American Society of Clinical Oncology (ASCO) (5) and the European Society for Medical Oncology (ESMO) (6); on the contrary, cryopreservation of ovarian tissue or cryopreservation of immature oocyte or of oocytes matured *in vitro* and temporary ovarian suppression with LHRHa are still considered experimental. The main factors that should be considered for the choice between the available fertility preservation techniques for young women candidates for anticancer therapies are: patient’s age and ovarian reserve, type of anticancer therapy planned, availability of a partner at the time of diagnosis, the time available before the initiation of anticancer treatments, and the possibility that cancer has metastasized to the ovaries (5).

Irrespective of the pro and contra of the different strategies, every young breast cancer patient who is candidate to anticancer therapies (particularly chemotherapy and endocrine therapy) should have access to fertility counseling to receive information about ovarian damage due to such treatments (5). Health care providers should be knowledgeable about guidelines on fertility preservation in patients with cancer diagnosed at young age: they have the responsibility to raise awareness on potential fertility impairment due to anti-cancer therapies and should be able to deal with these issues. Fertility counseling is the key moment to discuss the fertility issues before the time of treatment initiation: it should include a detailed description of all the available strategies to preserve fertility which are appropriate for that particular patient including techniques, timing, possible complications, success rates, costs and ethical implications (7). A major objective is to elucidate the patient about what is well-known and considered standard and what is still experimental about these techniques: more

than one strategy can sometimes be applied to the same patient to increase the chances of maintaining fertility and future pregnancies (7).

The available evidence suggests that infertility resulting from cancer treatment may be associated with psychosocial distress and negative impacts on global health of young breast cancer survivors (2,8). However, while the majority of data regarding fertility concerns in young women with breast cancer has focused on long-term survivors, little is known on the burden of fertility concerns at the time of breast cancer diagnosis before the initiation of anticancer treatments. Particularly, few data are available on the possible impact of fertility concerns on treatment decisions and about patients' preferences among the available strategies of fertility preservation.

The paper recently published by Ruddy and colleagues in the *Journal of Clinical Oncology* has a great importance in the understanding of the burden of fertility issues in young breast cancer patients at the time of diagnosis (9). The "Helping Ourselves, Helping Others: The Young Women's Breast Cancer Study" is a large prospective multicentre cohort study of young women with newly diagnosed stage I-III breast cancer and age ≤ 40 years. The primary endpoint of the study was the assessment of fertility concerns; other important objectives of the trial were the understanding of how fertility concerns affect treatment decisions and the preferences of women regarding the available fertility preservation strategies. Of the 1,511 women invited to participate between November 2006 and December 2012, only 620 were included in the final analysis. At the time of breast cancer diagnosis, the median age of the participants was 37 years (range, 17-40 years), 76% were married and 34% were childless. Regarding tumor characteristics, 58% were grade III, 29% were estrogen receptor-negative, 36% were progesterone receptor-negative and 30% were HER2-positive. A total of 424 women (68%) discussed fertility issues with their physicians before starting therapy: no increasing or decreasing trends in the likelihood of these discussions were shown over time between 2006 and 2012. At the time of decision making about treatment, 319 women (51%) had concerns about becoming infertile after treatment: again for fertility concerns, no change over time between 2006 and 2012 was shown. At the multivariable logistic regression model, the factors associated with greater statistically significant likelihood of fertility concerns were: age [age ≥ 35 *vs.* < 35 : odds ratio (OR) 0.26, 95% confidence interval (CI): 0.18-0.40, $P < 0.001$], race (white *vs.* not: OR 0.38, 95% CI: 0.20-0.72,

$P = 0.003$), receipt of chemotherapy (received chemotherapy *vs.* none: OR 1.61, 95% CI: 1.04-2.50, $P = 0.03$) and currently childless (has children *vs.* does not: OR 0.17, 95% CI: 0.11-0.26, $P < 0.001$). It is noteworthy that 112 patients (18%) reported that concerns about fertility affected their decisions regarding the medical treatment they would undergo: 4 women (1%) chose not to receive chemotherapy, 12 (2%) chose one chemotherapy over another, 6 (1%) considered not receiving endocrine therapy, 19 (3%) decided not to receive endocrine therapy, and 71 (11%) considered receiving endocrine therapy for < 5 years. Despite the great proportion of women concerned about fertility, few patients (65 women, 10%) took special steps to lessen their chance of infertility: 46 women (7%) underwent embryo cryopreservation, 7 (1%) oocyte cryopreservation and 19 (3%) accepted the administration of LHRHa during chemotherapy. The proportion of patients who pursued fertility preservation techniques seemed to increase over time (from 5% in 2006 to 15% in 2012) (9). In conclusion, the main findings of the study are that 32% of women did not discuss fertility issues with their physicians, 18% of women decided not to receive the proposed treatments because of fear of infertility and, despite the high proportion of women concerned about fertility, only 10% underwent one of the available strategies to preserve fertility.

It is well known that the fertility issues are not always dealt with appropriately by physicians thus depriving patients of the opportunity to access effective fertility preservation techniques (10). Fortunately, the data seems to be improving: a recent German study showed that the proportion of patients who could not remember proper counselling about the risk of fertility impairment due to anticancer treatments decreased significantly over time (11). In the years 1980-1984 the proportion of patients who reported no memories of counselling was 67% while in the years 2000-2004 decreased to 50% ($P < 0.001$) (11). Another recent Swedish study reported similar findings with less than half of women (48%) reporting to have received information about treatment impact on fertility and 14% who reported having received information about the available fertility preservation strategies (12). In the study by Ruddy *et al.*, fewer women, nearly one third (32%), did not discuss fertility issues with their physicians: however, as discussed by authors themselves, many women were enrolled at Institutions that focus particularly on care of young women, and so fertility discussions might be rarer and less substantive elsewhere (9). Several factors may hinder the discussion between the medical oncologists and

the patients: the fact that oncologists might not be aware of the clinical recommendations related to the issue of fertility preservation or not being update on the subject, the lack of ad hoc multi-disciplinary teams, and factors related to the patient (level of education, prognosis, sex, parental status, marital status, having children at diagnosis, age and pubertal status, economic opportunities) (13). Despite a trend towards a reduction in the number of women who do not receive fertility counseling at the time of diagnosis, more efforts should be made to continue to improve communication about fertility risks and options to preserve fertility.

Furthermore, an accurate communication has a great importance to avoid the possibility that concerns about the risk of infertility would have an impact on treatment decisions. In 2004, Partridge and colleagues reported that out of 657 young early breast cancer patients interviewed, 193 (29%) indicated that concerns about fertility impacted on their treatment decisions (14). Particularly, authors found that women who reported greater concern about fertility required greater risk reduction from chemotherapy and were much less likely to accept a higher risk of infertility from adjuvant chemotherapy than women who were less concerned about fertility (14). In the study by Ruddy *et al.* the proportion of patients who decided not to receive the initially prescribed treatments due to infertility concerns was lower but still significant (112/620 women, 18%) (9). However, although evidence suggests that some patients prefer to receive less effective treatments in order to prevent long-term complications such as infertility, many of them prefer not to deal with these concerns with their treating physicians. Then, it is up to the clinician to deliver limited information and delegating the task to other members of the multidisciplinary team, such as specialised nurses, whose role in this area is widely recognized (8).

Finally, despite a growing amount of evidence suggesting that fertility issues are of great importance for young women diagnosed with cancer, limited data exist about the proportion of patients who do make use of fertility preservation techniques. The percentage of patients who choose to undergo fertility preservation strategies (oocytes/embryos cryopreservation or ovarian tissue cryopreservation) after fertility counseling reported in the literature varies from 2% to over 50% (12,15). Ruddy and colleagues reported that out of 620 women, 65 (10%) took special steps to lessen chance of infertility (7% underwent embryo cryopreservation, 1% oocyte cryopreservation and 3% accepted the administration of LHRHa) but with an increasing trend over time in the

proportion of patients who pursued fertility preservation techniques (from 5% in 2006 to 15% in 2012) (9). Similar findings come from our experience: approximately 22% of breast cancer patients accepted to undergo fertility counseling performed by the reproductive physician and 8% underwent surgical fertility preservation techniques (oocytes cryopreservation or ovarian tissue cryopreservation) (7); however, a significant greater proportion of patients (85%) compared to the study by Ruddy *et al.* accepted to undergo the administration of LHRHa during chemotherapy, since this strategy is recommended by the Italian guidelines for fertility preservation in breast cancer patients (7). Despite a high proportion of young women with breast cancer reporting to be concerned about fertility, only a small proportion of them decide to undergo one of the available fertility preservation strategies. Possible explanations are: a lack of discussion of fertility issues between patients and physicians (as discussed above), concerns about the safety of these techniques, fear of a negative impact of pregnancy after breast cancer, and inadequate access to these strategies. Regarding the safety of the techniques, particularly for hormone responsive tumors, there are still some concerns about a possible negative impact of the ovarian stimulation required for oocyte and embryo cryopreservation. To try to reduce the potential risk of short-term exposure to high estrogen levels, alternative approaches for ovarian stimulation with letrozole or tamoxifen have been developed (16). As reported by Azim and colleagues in the largest experience with the use of cryopreservation strategies in breast cancer patients, at a median follow up of 23.4 months after chemotherapy, the hazard ratio for recurrence after *in vitro* fertilization was 0.56 (95% CI: 0.17-1.9) and the survival of patients that underwent cryopreservation strategies was not compromised compared with controls (17). However, further research, including longer-term follow-up for both cryopreservation strategies and for LHRHa administration, is needed to confirm the safety of these procedures. Another important point to keep in mind during fertility counseling is the fear of some patients (but also of some physicians) about the occurrence of congenital abnormalities and the potential obstetric and birth complications due to previous cancer treatments, and the theoretic risk that pregnancy might have negative consequences on patients' prognosis. The available evidence suggests that the occurrence of congenital abnormalities of infants born to women with a history of breast cancer is similar to that of the general population (6). On the other side, a relatively higher

incidence of birth complications (caesarean section, preterm birth, babies with low birth weight), in women previously treated for breast cancer as compared to the general population has been reported (18); therefore, a close monitoring of pregnancy in women previously treated for cancer is recommended. So far, it is well established that women who become pregnant after breast cancer do not have a worse prognosis: neither in young women with estrogen receptor-positive breast cancer any difference in DFS and OS has been observed between women who became pregnant after breast cancer and non-pregnant patients (19). Finally, it is mandatory for oncologists to cooperate with one or more Reproductive Units to give their patients the opportunity to undergo a well-timed and complete reproductive counseling. According to the results of a recent survey on post-treatment quality of life (QoL) in young women with cancer who were counseled either by the oncology team or by fertility specialists, the specialized counseling about reproductive loss and pursuing fertility preservation is associated with less regret and greater QoL for survivors (20). Therefore, a well-organized interaction between oncology and reproductive units is the first step to be accomplished to face the management of fertility issues in young cancer patients (7).

In summary, despite many young breast cancer patients have concerns about fertility at the time of diagnosis, only a minority undergo one of the available fertility preservation strategies and little over one-sixth change their therapeutic strategy. More efforts are needed to ameliorate the communication on the fertility issues in all women of reproductive age diagnosed with cancer to improve their opportunities to participate in informed decisions regarding their treatment and future reproductive ability. Future researches are needed to better understand the factors that influence patients' choice: these would help physicians to improve the quality of their fertility counseling.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Lambertini M, Pinto AC, Del Mastro L. Fertility issues in young breast cancer patients: what women want. *J Thorac Dis* 2014;6(6):584-588. doi: 10.3978/j.issn.2072-1439.2014.06.12