Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in youngBRCA-mutated breast cancer patients

Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients: results from the BCY3/BCC 2017 survey

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ABSTRACT

Background

In young *BRCA*-mutated breast cancer patients, fertility and pregnancy-related issues can be particularly overwhelming. No evidence exists on the knowledge, attitudes and practice of physicians towards these topics in young *BRCA*-mutated breast cancer patients.

Methods

Physicians attending the 2016 3rd ESO-ESMO Breast Cancer in Young Women Conference (BCY3) and the 15th St. Gallen International Breast Cancer Conference 2017 (BCC 2017) were asked to complete a 26-item questionnaire exploring fertility preservation, pregnancy after breast cancer and breast cancer during pregnancy (BCP). Some of the questions explored these topics in the specific subgroup of young *BRCA*-mutated breast cancer patients. A statistical comparison for the responses obtained from the questions exploring the same issues in young breast cancer patients overall or specifically in those with *BRCA* mutations was performed.

Results

The survey was completed by 273 physicians (105 at BCY3 and 168 at BCC 2017) with a median age of 46 years (range 38-55). A comparable proportion of respondents suggested the use of either embryo (43% vs. 39%; p=0.11) and/or oocyte (62% vs. 63%; p=0.77) cryopreservation as available options in *BRCA*-mutated patients or in the overall breast cancer population, respectively. Conversely, ovarian tissue cryopreservation (33% vs. 40%; p=0.009) and GnRHa during chemotherapy (74% vs. 81%; p=0.001) were less commonly suggested in *BRCA*-mutated breast cancer patients. 42% agreed or were neutral on the

statement that controlled ovarian stimulation should not be considered safe in *BRCA*-mutated breast cancer patients.

45% and 30% agreed or were neutral on the statement that pregnancy in BC survivors may increase the risk of recurrence in *BRCA*-mutated patients or in the overall breast cancer population, respectively ($p<0.001$). 15% and 3% disagreed that transplanting the cryopreserved ovarian tissue can be considered safe in *BRCA*-mutated patients or in the overall breast cancer population, respectively ($p<0.001$). 33.3% were against the addition of platinum agents as neoadjuvant chemotherapy in *BRCA*-mutated patients with BCP.

Conclusions

Several misconceptions on fertility preservation and pregnancy-related issues in breast cancer patients persist even among physicians directly involved in breast cancer care. Focused research efforts to address these issues in *BRCA*-mutated breast cancer patients and education to improve physicians´ knowledge and adherence to available guidelines are urgently needed.

MANUSCRIPT

Introduction

More than 10% of all breast malignancies arising in women diagnosed at ≤ 40 years of age are expected to be hereditary tumors related to germline deleterious mutations in the breast cancer susceptibility genes *BRCA1* or *BRCA2* [1]. Carrying a germline deleterious *BRCA* mutation significantly impact on the management of cancer prevention, diagnosis and treatment [2]. Moreover, there is a biologic rationale supported by preclinical evidence that these mutations can negatively impact also on female reproductive potential [3]. In cancer patients, this can have the possible added burden of increasing the risk of gonadotoxicity in women who are candidates to receive anticancer treatments during their reproductive age [3]. In addition, considering the significant lifetime risk of ovarian cancer [4], *BRCA* carriers are candidates to prophylactic gynecological surgery at a young age [2]. Hence, in young *BRCA*-mutated breast cancer patients, fertility and pregnancy-related issues can be particularly overwhelming [3].

In recent years, thanks to availability of a growing amount of data on these topics, specific guidelines on fertility preservation [5,6], pregnancy following anticancer treatments [5], and management of breast cancer diagnosed during pregnancy (BCP) [5,7] have been developed to help physicians in dealing with these important topics. However, limited evidence exists to support the current available recommendations in the counseling of young *BRCA*-mutated breast cancer patients facing fertility and pregnancy-related issues [2]. Several surveys exploring the reproductive decision-making and attitudes of *BRCA* carriers towards fertility preservation and childbearing habits have raised the awareness of the importance to implement the counseling of these women after test disclosure [8–10]. Nevertheless, there is

lack of data on physicians' perspectives and behavior around these topics in the specific cohort of *BRCA*-mutated breast cancer patients.

We have recently reported the results of our survey conducted among different specialists involved in breast cancer care who participated in two international breast cancer conferences exploring physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients [11]. Although the overall picture was positive and encouraging, we observed that adherence to guidelines around these topics remains sub-optimal [11]. In the present analysis, we analyzed the questions that explored physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in the specific subgroup of young *BRCA*-mutated breast cancer patients. We hypothesized a poorer performance of responding physicians on this regard considering the more limited available data to properly counsel *BRCA*-mutated patients in this setting.

Materials and methods

Details of this survey were previously reported [11]. Briefly, this was a 26-item questionnaire investigating fertility and pregnancy-related issues among physicians who attended the 2016 3rd ESO-ESMO Breast Cancer in Young Women Conference (BCY3) [12] and the 15th St. Gallen International Breast Cancer Conference 2017 (BCC 2017) [13]. Different specialists as well as non-medical personnel and advocates involved in breast cancer care participated in these conferences.

A specific questionnaire was prepared on the basis of prior surveys on these topics [14–16] that was then adapted to the BCY3/BCC 2017 context by a team of physicians specifically experienced in this field to include also some specific unaddressed questions. The survey

explored demographic, medical training and background information of responding physicians, as well as their knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer and BCP (Supplementary Appendix).

The survey was distributed electronically by email to all BCY3 and BCC 2017 participants but only physicians were allowed to complete it; for those who attended both the BCY3 and BCC 2017 conferences, only one access was allowed.

Study Objectives

The objective of the survey was to describe physicians' knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer, and BCP in young breast cancer patients [11].

The present analysis focuses on the questions exploring fertility and pregnancy-related issues in the specific subgroup of *BRCA*-mutated breast cancer patients.

Statistical analysis

Details on sample size calculation were previously reported [11]. The present analysis provided descriptive statistics on physicians' knowledge, attitudes and practice towards fertility preservation, pregnancy after breast cancer and BCP in young *BRCA*-mutated breast cancer patients.

A four-point Likert scale (from "not at all knowledgeable" to "very knowledgeable") or a five-point Likert scale (from "strongly disagree" to "strongly agree") were used to assess physicians' knowledge, attitudes and practice around these topics. The answers "strongly

agree" and "agree" as well as "strongly disagree" and "disagree" were grouped together when a five-point Likert scale was used to assess physicians' knowledge, attitudes and practice.

The main analysis was conducted by pooling the answers obtained from both the BCY3 and BCC 2017 conferences. An exploratory statistical comparison of the answers obtained individually in the two events was also performed considering the potentially different professional profile of physicians who participated in the two conferences (Supplementary Appendix).

When the same question explored a specific issue in both breast cancer patients overall and specifically in those with *BRCA* mutations, a formal statistical comparison was conducted to investigate potential differences in the knowledge, attitudes and practice towards these issues in the two populations of breast cancer patients.

The Wilcoxon-Mann-Whitney test was applied to assess differences in participants' age and years of clinical practice, while the Chi2-test was used for exploring differences between the two conferences in categorical variables and answers. McNemar test for paired proportions was applied for the comparison between the responses in *BRCA*-mutated patients or in the overall breast cancer population.

All tests were two-sided and p-values < 0.05 were considered statistically significant. SPSS for Windows Version 24.0 was used for all statistical analyses.

Results

At the BCY3 conference, 124 (45.1%) out of 275 participants accessed the survey of whom 19 were not physicians leaving 105 completed questionnaires to be included. At the BCC

2017 conference, 210 (7.0%) out of approximately 3000 participants accessed the survey of whom 20 were not physicians and 22 had previously filled in the BCY3 survey leaving 168 completed questionnaires to be included. Therefore, all the analyses were conducted with a sample size of 273 responding physicians.

As shown in Table 1, the respondents had a median age of 46 years (interquartile range 38-55); more physicians who attended the BCC 2017 conference were older than 50 years as compared to those participating in the BCY3 conference (42.3% vs. 23.8%; p=0.001). A total of 57.1% of responding physicians were female with a higher proportion among physicians attending the BCY3 conference (67.6% vs. 50.6%; p=0.006). The majority of respondents came from Western Europe (56.4%) with a higher proportion from America among those who attended the BCC 2017 conference (17.3% vs. 6.7%; p=0.004). Most of the responding physicians were medical oncologists (53.8%) working in dedicated breast unit (81.7%) and in an academic setting (86.1%).

Fertility issue

A similar proportion of responding physicians reported to always or usually suggests the use of embryo cryopreservation (42.9% vs. 39.2%; p=0.11; Figure 1A) and/or oocyte cryopreservation (62.3% vs. 63.3%; p=0.77; Figure 1B) as a strategy for fertility preservation in *BRCA*-mutated patients or in the overall breast cancer population, respectively.

On the contrary, significant differences were reported for the other two strategies. Specifically, 32.9% and 40.0% (p=0.009; Figure 1C) of respondents reported to always or usually suggest ovarian tissue cryopreservation in *BRCA*-mutated patients or in the overall breast cancer population, respectively. Temporary ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy was the most commonly

suggested strategy overall, but with a significant lower number of responding physicians that reported to always or usually suggest its use in patients with *BRCA*-mutated breast cancer (74.0% vs. 81.0%; p=0.001; Figure 1D).

No significant difference between the BCY3 and the BCC 2017 participants was observed in the attitudes towards the different strategies (Appendix Table A1).

Overall, 42 (15.4%) respondents suggested that controlled ovarian hyperstimulation (COH) for embryo/oocyte cryopreservation should not be considered safe in the specific subgroup of *BRCA*-mutated breast cancer patients, while 73 (26.7%) were neutral and 158 (57.9%) disagreed with this statement; there was no significant difference between the BCY3 and the BCC 2017 participants (Appendix Table A1).

Pregnancy-related issues

Eighty-three (30.4%) and 124 (45.5%) respondents agreed or were neutral on the statement that a pregnancy in breast cancer survivors may increase the risk of recurrence overall and in *BRCA*-mutated breast cancer patients, respectively (p<0.001; Figure 2A).

A total of 25 (9.2%) responding physicians were in favor and 69 (25.3%) were neutral towards the statement that a pregnancy in *BRCA*-mutated breast cancer survivors should be discouraged due to the risk in transmitting the mutated gene to the baby. Fourteen (5.1%) and 85 (31.1%) respondents disagreed or were neutral on the statement that information about pre-implantation genetic diagnosis should be given to these women.

Table 2 reports the knowledge, attitudes and practice of physicians towards different aspects of managing breast cancer patients overall or specifically those with a *BRCA*-mutation having pregnancy desire. No significant differences were observed in terms of number of

respondents who agreed about the safety of breastfeeding as well as use of assisted reproductive technology including COH and egg donation in young *BRCA*-mutated survivors or in the overall breast cancer population. On the contrary, a different attitude was observed towards the safety of proceeding to auto-transplantation of the cryopreserved ovarian tissue harvested at the time of cancer diagnosis with 41 (15.0%) respondents that disagreed about the safety of this approach in *BRCA*-mutated breast cancer survivors as compared to 8 (2.9%) in the overall breast cancer population ($p<0.001$; Figure 2B)

Regarding the management of BCP, 214 (78.4%) responding physicians were in favor of the use of chemotherapy in the 2nd and 3rd trimesters of pregnancy. The only question specifically focused to *BRCA*-mutated patients with BCP investigated the attitude of physicians towards the addition of a platinum agent as neoadjuvant chemotherapy in these women. The majority of respondents (114, 41.8%) were neutral towards this statement, 68 (24.9%) were in favor of its use while 91 (33.3%) were against the addition of these agents.

No significant difference between the BCY3 and the BCC 2017 participants was observed in the attitudes towards pregnancy-related issues in *BRCA*-mutated breast cancer patients (Appendix Table A2).

Discussion

To our knowledge, this is the first survey among physicians with specific interest in breast cancer care to explore their knowledge, attitudes and practice towards fertility preservation and pregnancy-related issue in the specific subgroup of young *BRCA*-mutated breast cancer patients. Overall, our survey showed some peculiarities in physicians' perspectives and behavior around these topics in the subgroup of *BRCA*-mutated breast cancer patients

reflecting the limited knowledge and evidence available on this regard to specifically counsel these women.

According to current guidelines, all women with a new cancer diagnosis during their reproductive years who are concerned about the gonadotoxicity of the proposed anticancer treatments should be offered the available strategies for ovarian function and/or fertility preservation [5,6,12]. However, notably, the adherence to these guidelines remains suboptimal [11] and no specific recommendations exist for counseling *BRCA*-mutated breast cancer patients [3].

Embryo and oocyte cryopreservation are the first strategies to be offered to patients interested in fertility preservation including *BRCA* carriers [5,6,12]. No difference in the proportion of physicians suggesting the use of these options in *BRCA*-mutated patients or in the overall breast cancer population was observed but the rates of those who always or usually propose these strategies remained quire low (39-43% for embryo cryopreservation and 62-63% for oocyte cryopreservation). These findings may reflect the still limited efficacy [17,18] and safety [19–21] data available on these strategies in cancer patients particularly for counseling *BRCA* carriers [3]. Importantly, embryo and oocyte cryopreservation would allow the access to pre-implantation genetic diagnosis. Of note, two of the three studies that have investigated specifically the performance of embryo and oocyte cryopreservation in young breast cancer patients carrying a *BRCA* mutation showed a possible lower response to COH in these women as compared to those without mutations [22–24]. However, the numbers remain too limited to draw conclusions on the need for personalized COH protocols in *BRCA*-mutated patients [3]. From a safety perspective, we observed that 42.1% of the respondents agreed or were neutral on the statement that COH for embryo/oocyte cryopreservation should not be considered safe in the specific subgroup of *BRCA*-mutated breast cancer patients.

Nevertheless, the available but limited data on this regard do not support these concerns. Among the 47 *BRCA*-mutated patients included in the study by Kim and colleagues, no significant difference in relapse-free survival was observed between women who underwent COH and those who did not pursue any fertility-preserving procedure [19].

A different attitude of physicians was observed towards the use of ovarian tissue cryopreservation and temporary ovarian suppression with GnRHa during chemotherapy, with a significant lower percentage of respondents that replied to always or usually suggest their use in *BRCA*-mutated patients. These findings reflect the specific considerations that should be made around these two options in the subgroup of *BRCA*-mutated patients. Despite being still considered an experimental strategy in most of the countries [5,6,12], ovarian tissue cryopreservation should now be considered an option for selected patients including some young women with breast cancer [25] considering the recent availability of a growing amount of data on its efficacy [26]. However, only two live births have been described after ovarian tissue transplantation in *BRCA*-mutated breast cancer patients [23,27]. Based on recent data reporting the efficacy and safety of this strategy in preserving ovarian function and potential fertility [28,29], temporary ovarian suppression with GnRHa during chemotherapy is now considered an option to be discussed with young breast cancer patients [6,12,30]. However, there are no specific data on its performance in *BRCA*-mutated breast cancer patients. Besides the limited or lack of evidence on these options for *BRCA* carriers, it should be highlighted that both ovarian tissue cryopreservation and temporary ovarian suppression with GnRHa during chemotherapy are not optimal strategies in this setting particularly among women who are diagnosed close to the recommended age of prophylactic gynecological surgery [3]. In our survey, a significantly higher number or respondents (up to 15%) considered not safe proceeding to auto-transplantation of the cryopreserved ovarian tissue harvested at the time of cancer diagnosis in *BRCA* carriers as compared to the overall breast cancer population.

Importantly, to reduce these concerns when the transplantation procedure is performed in *BRCA*-mutated patients, the ovarian fragments should be transplanted directly into the remaining gonads so that all ovarian tissue can be removed after completing the reproductive plans [23].

Despite a significant proportion of young breast cancer survivors desire to complete their family planning [31–33], their chances of conceiving remain significantly lower as compared to those of the general non-oncologic population [5]. This can be also partly explained by the safety concerns shared by both patients and their treating physicians on the potential negative prognostic effect of having a pregnancy following breast cancer [11,34,35]. Our survey showed that these concerns are significantly more important towards *BRCA*-mutated breast cancer patients with up to 45.5% of respondents that agreed or were neutral on the statement that a pregnancy in this setting may increase the risk of recurrence. Recently, a growing amount of data have supported the safety of having a pregnancy in breast cancer survivors after adequate treatment and follow-up [36–39]. However, the evidence on this regard for *BRCA* carriers relies only on a small retrospective cohort study showing no difference in breast cancer specific mortality among *BRCA*-mutated patients with or without a pregnancy after prior history of breast cancer [40]. In addition, while limited data are available in the breast cancer population on the safety and feasibility of breastfeeding [38] and on the use of assisted reproductive technology procedures in breast cancer survivors [41], no specific evidence on this topic exists for *BRCA* carriers. This probably explains the neutral answers of approximately 30% of the responding physicians on the statements that investigated these issues in both breast cancer patients overall and in *BRCA* carriers. Additional research efforts including the ongoing POSITIVE trial (IBCSG 48-14 NCT02308085) [42] are needed to provide more definitive answers on the several unanswered issues in this field. Finally, in

BRCA-mutated breast cancer survivors interested in conceiving, we observed that a high percentage of respondents (36.2%) disagreed or were neutral on the statement that information about pre-implantation genetic diagnosis should be given to these women. Although the reasons for these findings were not assessed in our survey, recent data suggest that lack of physicians' awareness and knowledge about pre-implantation genetic diagnosis may represent an important barrier to discuss this option and refer interested patients [43].

Regarding the management of patients with BCP, in recent years, several studies have provided evidence on the feasibility and safety of administering chemotherapy during the second and third trimesters of pregnancy [44,45]. In this period, the use of both anthracycline-based chemotherapy and taxanes is allowed by current guidelines [5,7]. The use of platinum agents in *BRCA*-mutated breast cancer patients is now considered standard of care in the metastatic setting [46] but remains controversial in the early setting [12,13]. In fact, while the addition of a platinum agent to anthracycline- and taxane-based chemotherapy showed to significantly improve the rate of pathological complete response in patients with triple-negative breast cancer, no clear benefit was observed for the cohort of *BRCA* carriers [47]. Although platinum-based chemotherapy is not contraindicated in pregnant patients [5,7], evidence deriving mainly from the treatment of women with malignancies other than breast cancer suggests an increased risk of small for gestational age with in utero exposure to these agents [48]. These data together with the unclear benefit of using platinum-based chemotherapy in the neoadjuvant setting may explain the high proportion of responding physicians that were neutral (41.8%) or disagreed (33.3%) on the need to include these agents in *BRCA*-mutated patients with BCP.

A few limitations should be considered in the interpretation of our findings including the low response rate during the BCC 2017 congress [11]. In addition, the specific target of our survey (i.e. physicians with specific interest in breast cancer care and thus expected to have higher than average knowledge on these issues and willingness to discuss them) should be highlighted for better interpreting our results. Most of the respondents were medical oncologists working in Western Europe, dedicated breast unit and in an academic setting. We did not collect information on the knowledge, attitudes and practice towards these issues of nursing staff, patients or caregivers. However, this was indeed the main intent of our study focused to a selected population of physicians to allow an even better interpretation of the challenges and the needs for further education required for managing fertility and pregnancy-related issues in young breast cancer patients.

In conclusion, results from the BCY3/BCC 2017 survey focused on fertility preservation and pregnancy-related issues in young *BRCA*-mutated breast cancer patients highlight the presence of several misconceptions on these topics that persist even among physicians directly involved in breast cancer care. Focused research efforts to address the several existing grey zones in the field and education to improve physicians' knowledge and adherence to available guidelines are urgently needed to improve the oncofertility counselling of young *BRCA*-mutated breast cancer patients.

Conflict of interest and funding

Matteo Lambertini served as a consultant for Teva outside the submitted work. Hatem A. Azim Jr. reports employment at Innate Pharma at the end of this study; this employment is not related in any sort to the subject of the current study. All remaining authors declare no conflict of interest. No funding were received for the conduction of this study.

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References

1. Rosenberg SM, Ruddy KJ, Tamimi RM, Gelber S, Schapira L, Come S, et al. BRCA1 and BRCA2 Mutation Testing in Young Women With Breast Cancer. JAMA Oncol. 2016 Jun 1;2(6):730–6.

2. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol Off J Eur Soc Med Oncol. 2016 Sep;27(suppl 5):v103–10.

3. Lambertini M, Goldrat O, Toss A, Azim HA, Peccatori FA, Ignatiadis M, et al. Fertility and pregnancy issues in BRCA-mutated breast cancer patients. Cancer Treat Rev. 2017 Sep;59:61–70.

4. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips K-A, Mooij TM, Roos-Blom M-J, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 20;317(23):2402–16.

5. Peccatori FA, Azim HA Jr, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol ESMO. 2013 Oct;24 Suppl 6:vi160-170.

6. Oktay K, Harvey BE, Partridge AH, Quinn GP, Reinecke J, Taylor HS, et al. Fertility

Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol Off J Am Soc Clin Oncol. 2018 Jul 1;36(19):1994–2001.

7. Loibl S, Schmidt A, Gentilini O, Kaufman B, Kuhl C, Denkert C, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol. 2015 Nov;1(8):1145–53.

8. Woodson AH, Muse KI, Lin H, Jackson M, Mattair DN, Schover L, et al. Breast cancer, BRCA mutations, and attitudes regarding pregnancy and preimplantation genetic diagnosis. The Oncologist. 2014 Aug;19(8):797–804.

9. Chan JL, Johnson LNC, Sammel MD, DiGiovanni L, Voong C, Domchek SM, et al. Reproductive Decision-Making in Women with BRCA1/2 Mutations. J Genet Couns. 2017 Jun;26(3):594–603.

10. Gietel-Habets JJG, de Die-Smulders CEM, Derks-Smeets I a. P, Tibben A, Tjan-Heijnen VCG, van Golde R, et al. Awareness and attitude regarding reproductive options of persons carrying a BRCA mutation and their partners. Hum Reprod Oxf Engl. 2017 Mar 1;32(3):588–97.

11. Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, Del Mastro L, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast Edinb Scotl. 2018 Aug 22;42:41–9.

12. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso M-J, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). Breast Edinb Scotl. 2017 Oct;35:203–17.

13. Curigliano G, Burstein HJ, P Winer E, Gnant M, Dubsky P, Loibl S, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann

Oncol Off J Eur Soc Med Oncol. 2017 Aug 1;28(8):1700–12.

14. Quinn GP, Vadaparampil ST, Lee J-H, Jacobsen PB, Bepler G, Lancaster J, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. J Clin Oncol Off J Am Soc Clin Oncol. 2009 Dec 10;27(35):5952–7.

15. Forman EJ, Anders CK, Behera MA. A nationwide survey of oncologists regarding treatment-related infertility and fertility preservation in female cancer patients. Fertil Steril. 2010 Oct;94(5):1652–6.

16. Adams E, Hill E, Watson E. Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes. Br J Cancer. 2013 Apr 30;108(8):1602–15.

17. Oktay K, Turan V, Bedoschi G, Pacheco FS, Moy F. Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Aug 1;33(22):2424–9.

18. Massarotti C, Scaruffi P, Lambertini M, Remorgida V, Del Mastro L, Anserini P. State of the art on oocyte cryopreservation in female cancer patients: A critical review of the literature. Cancer Treat Rev. 2017 Jun;57:50–7.

19. Kim J, Turan V, Oktay K. Long-Term Safety of Letrozole and Gonadotropin Stimulation for Fertility Preservation in Women With Breast Cancer. J Clin Endocrinol Metab. 2016 Apr;101(4):1364–71.

20. Rodriguez-Wallberg KA, Eloranta S, Krawiec K, Lissmats A, Bergh J, Liljegren A. Safety of fertility preservation in breast cancer patients in a register-based matched cohort study. Breast Cancer Res Treat. 2017 Nov 2;

21. Lambertini M, Fontanella C. How reliable are the available safety data on hormonal stimulation for fertility preservation in young women with newly diagnosed early breast cancer? Breast Cancer Res Treat. 2018 Apr;168(3):773–4.

22. Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, et al. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertil Steril. 2015 Nov;104(5):1162–7.

23. Lambertini M, Goldrat O, Ferreira AR, Dechene J, Azim HA, Desir J, et al. Reproductive potential and performance of fertility preservation strategies in BRCA-mutated breast cancer patients. Ann Oncol Off J Eur Soc Med Oncol. 2018 Jan 1;29(1):237–43.

24. Turan V, Bedoschi G, Emirdar V, Moy F, Oktay K. Ovarian Stimulation in Patients With Cancer: Impact of Letrozole and BRCA Mutations on Fertility Preservation Cycle Outcomes. Reprod Sci Thousand Oaks Calif. 2018 Jan;25(1):26–32.

25. Lambertini M, Del Mastro L, Pescio MC, Andersen CY, Azim HA, Peccatori FA, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016 Jan 4;14:1.

26. Pacheco F, Oktay K. Current Success and Efficiency of Autologous Ovarian Transplantation: A Meta-Analysis. Reprod Sci Thousand Oaks Calif. 2017 Aug;24(8):1111–20.

27. Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. J Assist Reprod Genet. 2017 Mar;34(3):325–36.

28. Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol Off J Eur Soc Med Oncol. 2015 Dec;26(12):2408–19.

29. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, Bruzzone M, et al. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of

Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol Off J Am Soc Clin Oncol. 2018 Jul 1;36(19):1981–90.

30. Lambertini M, Cinquini M, Moschetti I, Peccatori FA, Anserini P, Valenzano Menada M, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: A GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. Eur J Cancer Oxf Engl 1990. 2017 Jan;71:25–33.

31. Letourneau JM, Ebbel EE, Katz PP, Katz A, Ai WZ, Chien AJ, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. Cancer. 2012 Mar 15;118(6):1710–7.

32. Ruddy KJ, Gelber SI, Tamimi RM, Ginsburg ES, Schapira L, Come SE, et al. Prospective study of fertility concerns and preservation strategies in young women with breast cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2014 Apr 10;32(11):1151–6.

33. Pagani O, Bagnardi V, Ruggeri M, Bianco N, Gallerani E, Buser K, Giordano M, Gianni L, Rabaglio M, Freschi A, Cretella E, Clerico M, Amadori D, Simoncini E, Ciccarese M, Rauch D, Rosti G, Glaus A, Berardi R, Franzetti Pellanda A, Ruddy KJ, Gelber S, Partridge AH, Colleoni M. HOHO Study (IBCSG 43-09): how European and US young women cope with breast cancer and fertility concerns. Cancer Research 2017; 77(4 Supplement): abstract PD6-04-PD6-04.

34. Senkus E, Gomez H, Dirix L, Jerusalem G, Murray E, Van Tienhoven G, et al. Attitudes of young patients with breast cancer toward fertility loss related to adjuvant systemic therapies. EORTC study 10002 BIG 3-98. Psychooncology. 2014 Feb;23(2):173–82.

35. Biglia N, Torrisi R, D'Alonzo M, Codacci Pisanelli G, Rota S, Peccatori FA.

Attitudes on fertility issues in breast cancer patients: an Italian survey. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2015 Jun;31(6):458–64.

36. Hartman EK, Eslick GD. The prognosis of women diagnosed with breast cancer before, during and after pregnancy: a meta-analysis. Breast Cancer Res Treat. 2016 Nov;160(2):347–60.

37. Iqbal J, Amir E, Rochon PA, Giannakeas V, Sun P, Narod SA. Association of the Timing of Pregnancy With Survival in Women With Breast Cancer. JAMA Oncol. 2017 May 1;3(5):659–65.

38. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. J Natl Cancer Inst. 2018 Apr 1;110(4):426–9.

39. Lambertini M, Martel S, Campbell C, Guillaume S, Hilbers FS, Schuehly U, Korde L, Azim HA Jr., Di Cosimo S, Tenglin RC, Huober J, Baselga J, Moreno-Aspitia A, Piccart M, Gelber RD, de Azambuja E, Ignatiadis M. Pregnancies during and following trastuzumab and/or lapatinib in patients with HER2-positive early breast cancer: analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. Cancer. 2018; [Epub ahead of print].

40. Valentini A, Lubinski J, Byrski T, Ghadirian P, Moller P, Lynch HT, et al. The impact of pregnancy on breast cancer survival in women who carry a BRCA1 or BRCA2 mutation. Breast Cancer Res Treat. 2013 Nov;142(1):177–85.

41. Goldrat O, Kroman N, Peccatori FA, Cordoba O, Pistilli B, Lidegaard O, et al. Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. Eur J Cancer Oxf Engl 1990. 2015 Aug;51(12):1490–6.

42. Pagani O, Ruggeri M, Manunta S, Saunders C, Peccatori F, Cardoso F, et al. Pregnancy after breast cancer: Are young patients willing to participate in clinical studies? Breast Edinb Scotl. 2015 Jun;24(3):201–7.

43. Gietel-Habets JJG, de Die-Smulders CEM, Tjan-Heijnen VCG, Derks-Smeets I a. P, van Golde R, Gomez-Garcia E, et al. Professionals' knowledge, attitude and referral behaviour of preimplantation genetic diagnosis for hereditary breast and ovarian cancer. Reprod Biomed Online. 2018 Feb;36(2):137–44.

44. Loibl S, Han SN, von Minckwitz G, Bontenbal M, Ring A, Giermek J, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol. 2012 Sep;13(9):887–96.

45. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, et al. Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. N Engl J Med. 2015 Nov 5;373(19):1824–34.

46. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol Off J Eur Soc Med Oncol. 2018 Aug 1;29(8):1634–57.

47. Poggio F, Bruzzone M, Ceppi M, Pondé NF, La Valle G, Del Mastro L, et al. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Ann Oncol Off J Eur Soc Med Oncol. 2018 Jul 1;29(7):1497–508.

48. de Haan J, Verheecke M, Van Calsteren K, Van Calster B, Shmakov RG, Mhallem Gziri M, et al. Oncological management and obstetric and neonatal outcomes for women diagnosed with cancer during pregnancy: a 20-year international cohort study of 1170 patients. Lancet Oncol. 2018 Mar;19(3):337–46.

FIGURE LEGEND

Figure 1. Physicians' prescription of the different strategies for fertility preservation in *BRCA*-mutated patients or in the overall breast cancer population: 1) embryo cryopreservation; 2) oocyte cryopreservation; 3) ovarian tissue cryopreservation; temporary ovarian suppression with GnRHa during chemotherapy.

GnRHa=gonadotropin-releasing hormone analogs.

Figure 2. Physicians' attitudes toward pregnancy after breast cancer (A) and transplantation of cryopreserved ovarian tissue (B) in *BRCA*-mutated patients or in the overall breast cancer population.