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**The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice on fertility and pregnancy-related issues in young breast cancer patients**

Matteo Lambertini<sup>1</sup>, Massimo Di Maio<sup>2</sup>, Olivia Pagani<sup>3</sup>, Giuseppe Curigliano<sup>4</sup>, Francesca Poggio<sup>1,5</sup>, Lucia Del Mastro<sup>5</sup>, Shani Paluch-Shimon<sup>6</sup>, Sibylle Loibl<sup>7</sup>, Ann H. Partridge<sup>8</sup>, Isabelle Demeestere<sup>9</sup>, Hatem A. Azim Jr.<sup>10,\*</sup>, Fedro A. Peccatori<sup>11,\*</sup>

\* co-last authors

<sup>1</sup> Department of Medical Oncology and Breast Cancer Translational Research Laboratory, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

<sup>2</sup> Medical Oncology, A.O. Ordine Mauriziano, Department of Oncology, University of Turin, Turin, Italy

<sup>3</sup> Istituto Oncologico della Svizzera Italiana, Lugano, Switzerland

<sup>4</sup> New Drugs and Early Drug Development for Innovative Therapies, European Institute of Oncology, European School of Oncology (ESO), Milan, Italy

<sup>5</sup> Department of Medical Oncology, U.O. Sviluppo Terapie Innovative, Policlinico San Martino-IST, Genova, Italy

<sup>6</sup> Shaare Zedek Medical Centre, Jerusalem, Israel

<sup>7</sup> German Breast Group (GBG), Neu-Isenburg, and Centre for Haematology and Oncology, Frankfurt, Germany

<sup>8</sup> Department of Medical Oncology, Dana-Farber Cancer Institute, Boston (MA), USA

<sup>9</sup> Fertility Clinic, Research Laboratory on Human Reproduction, Erasme and Université Libre de Bruxelles (U.L.B.), Brussels, Belgium

<sup>10</sup> Department of Medicine, Division of Hematology/Oncology, American University of Beirut (AUB), Beirut, Lebanon

<sup>11</sup> Fertility and Procreation Unit, Gynecologic Oncology Department, European Institute of Oncology, European School of Oncology (ESO), Milan, Italy

**Corresponding author:**

Matteo Lambertini, MD

Department of Medical Oncology and Breast Cancer Translational Research Laboratory

Institut Jules Bordet and Université Libre de Bruxelles (U.L.B.)

1 Rue Héger Bordet, B-1000 Brussels, Belgium

Mail : [matteo.lambertini85@gmail.com](mailto:matteo.lambertini85@gmail.com) - [matteo.lambertini@bordet.be](mailto:matteo.lambertini@bordet.be)

Phone : +32 (0)2 541 3099

Fax : +32 (0)2 541 3339

## **ABSTRACT**

### **Background**

Fertility and pregnancy-related issues are areas of major concern for young breast cancer patients. Limited data are available on physicians' knowledge, attitudes and practice towards these issues in young breast cancer patients.

### **Material and methods**

A 26-item questionnaire exploring 3 different topics (fertility preservation, pregnancy after breast cancer and breast cancer during pregnancy [BCP]) was sent by email to physicians attending the 2016 3<sup>rd</sup> ESO-ESMO Breast Cancer in Young Women Conference (BCY3) and the 2017 15<sup>th</sup> St. Gallen International Breast Cancer Conference (BCC 2017). Given the selected sample, survey respondents were expected to have a higher than average interest in the management of BC patients. Descriptive analyses were performed.

### **Results**

A total of 273 physicians (105 at BCY3 and 168 at BCC 2017) completed the survey. Median age was 46 years (interquartile range 38-55). Among the respondents, 37.0%, 46.9% and 34.8% reported never having consulted the available international guidelines on fertility preservation, pregnancy after breast cancer and management of BCP, respectively.

Up to 18.3% of respondents did not know if the different fertility preservation options were available in their country. Ovarian suppression with gonadotropin-releasing hormone analogs during chemotherapy was the most commonly suggested strategy (81.0%). 43.2% of respondents disagreed or were neutral on the statement that controlled ovarian stimulation (COS) can be considered safe in breast cancer patients.

A total of 30.4% and 37.0% of the respondents agreed or were neutral on the statement that pregnancy in BC survivors may increase the risk of recurrence overall or only in those with hormone receptor-positive disease, respectively.

Regarding BCP, 26.0% of respondents believed that preterm delivery is the preferred option for patients diagnosed at the beginning of 3<sup>rd</sup> trimester of pregnancy in order to start chemotherapy in the post-partum period. 23.8% and 38.1% disagreed or were neutral on the statement that endocrine therapy and anti-HER2 agents should be avoided during pregnancy, respectively.

## **Conclusions**

These results highlight the need for further educational initiatives to improve physicians' knowledge and adherence to available guidelines when addressing fertility and pregnancy-related issues with young breast cancer patients.

## MANUSCRIPT

### Introduction

In women of reproductive age, breast cancer is the most commonly diagnosed malignancy and it's considered a public health problem due to its unique age-related medical and psychosocial challenges [1]. Among them, fertility and pregnancy-related issues are prevalent areas of concern in young breast cancer patients [2]. In these women, the gonadotoxic effect of anticancer treatments can lead to the potential development of premature ovarian insufficiency (POI) and infertility [3]. This is of major concern given the current trend of postponing pregnancy to later in life, and thus an increasing proportion of young women with breast cancer is expected to be diagnosed before completing their family plans [2]. In addition, for the same reason, an increased awareness should be paid to the possible diagnosis of breast cancer during pregnancy (BCP) whose possible occurrence also increases with age [4].

Over the past years, several research efforts have provided important evidence to support the management of patients facing fertility and pregnancy-related issues. Specific guidelines have been developed to help physicians in dealing with issues related to fertility preservation in cancer patients [5,6], pregnancy following anticancer treatments [5], and management of women diagnosed during pregnancy [4,5]. However, several controversies still exist in these fields and some physicians are still uncomfortable dealing with these issues [7,8]. Failure to adequately address these concerns in a timely manner can negatively impact not only on patients' short- and long-term quality of life but also on their adherence to the proposed anticancer treatments and subsequent disease outcomes [1].

To further explore the current knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young breast cancer patients, we performed a survey among different specialists involved in breast cancer care who participated in two international breast cancer conferences. To our knowledge, this is the first and only survey that aimed precisely to survey a selected group of physicians with specific interest in the management of breast cancer patients on three different relevant topics: fertility preservation, pregnancy after breast cancer and BCP.

### **Materials and methods**

This was a questionnaire survey investigating fertility and pregnancy-related issues among physicians who attended the 2016 3<sup>rd</sup> ESO-ESMO Breast Cancer in Young Women Conference (BCY3) held in Lugano (Switzerland) on November 10-12, 2016 [2], and those who participated in the 15<sup>th</sup> St. Gallen International Breast Cancer Conference 2017 (BCC 2017) that took place in Vienna (Austria) on March 15-18, 2017 [9].

Physicians from different specialties (medical oncologists, radiation oncologists, surgical oncologists, gynaecologists, fertility specialists, geneticists, etc) along with non-medical personnel involved in the management of breast cancer patients were expected to participate in these conferences.

### *Study Objectives*

The objective of the present survey was to describe physicians' knowledge, attitudes and practice on three different relevant issues in young breast cancer patients: a) fertility preservation, b) pregnancy after breast cancer, and c) BCP.

Most of the questions referred to young women with breast cancer as a whole with some of them that addressed the same issues in the specific subgroup of *BRCA*-mutated patients. The results of the questions focused on fertility and pregnancy-related issues in young *BRCA*-mutated breast cancer patients will be reported separately.

### *Characteristics of the survey*

The 26-item survey was divided in 4 main sections that explored, respectively (Appendix): 1) demographic, medical training and background information; 2) knowledge, attitudes and practice towards fertility preservation in breast cancer patients; 3) knowledge, attitudes and practice towards pregnancy after breast cancer; 4) knowledge, attitudes and practice towards BCP.

The knowledge of physicians towards these topics was investigated in some cases using a four-point Likert scale from “not at all knowledgeable” to “very knowledgeable”. In others, physicians’ knowledge as well as their attitudes and practice towards controversial items in these areas were assessed using a five-point Likert scale from “strongly disagree” to “strongly agree”.

### *Study procedures*

A 26-item questionnaire was developed on the basis of prior surveys on these topics conducted both in Europe and the United States [10–12]. The same items were used in some circumstances with adaptation to the BCY3/BCC 2017 context in others. The survey questions were prepared by a group of physicians comprising medical oncologists, gynaecologists and fertility specialists who are specifically experienced in the topic of



fertility preservation and management of pregnancy-related issues in young breast cancer patients.

The final survey was distributed electronically via email to the participants attending the BCY3 and BCC 2017 conferences. After accessing the online platform, only physicians were then allowed to access and to fill in the survey; for physicians who attended both conferences, a second access to complete the survey at the time of the BCC 2017 conference was not permitted.

### *Statistical analysis*

The sample size calculation was originally based on the number of participants to the BCY3 conference. Estimating a population (i.e. number of participants to the BCY3 conference) equal to 300, we aimed to obtain a sample size (i.e. number of respondents to the survey) of at least 100-150 physicians. In the case of a 2-category grouping of answers, a number of 100 respondents would allow a margin of error in the estimate of the proportion of approximately  $\pm 8\%$  with a 95% confidence level; a number of 150 respondents would allow a margin of error in the estimate of the proportion of  $\pm 5.67\%$ , with a 95% confidence level.

These numbers were considered sufficient to obtain information on these topics and to identify any items worthy of further research or need for education. Nevertheless, to acquire more robust data and further validate the consistency of these results, the survey was then repeated during the BCC 2017 conference.

The main analyses were performed by pooling the answers obtained from both the BCY3 and BCC 2017 conferences. The results obtained individually in the two events are presented

separately in the appendix; for each item of the survey, an exploratory statistical comparison of the answers obtained in the two conferences was also performed.

Primary analyses were descriptive. To explore differences in participants' age and years of clinical practice between the two conferences, Wilcoxon-Mann-Whitney test was applied; to explore differences between the two conferences in categorical variables and answers, Chi2-test was applied. When a five-point Likert scale was used to assess physicians' knowledge, attitudes and practice, the answers "strongly disagree" and "disagree" as well as "strongly agree" and "agree" were grouped together.

All tests were two-sided and p-values of  $< 0.05$  were considered statistically significant. All analyses were performed using SPSS for Windows Version 24.0.

## **Results**

Out of 275 participants attending the BCY3 conference, 124 (45.1%) accessed the survey of whom 19 were not physicians leaving a total of 105 eligible completed questionnaires. Among the ... participants attending the BCC 2017 conference, 210 (...%) accessed the survey of whom 20 were not physicians and 22 had already completed the BCY3 survey leaving a total of 168 eligible completed questionnaires. Hence, the main analyses were performed including a sample of 273 responding physicians.

The demographic, medical training and background information of the respondents is reported in Table 1. Median age was 46 years (interquartile range 38-55); the majority of the respondents were female (57.1%), from Western Europe (56.4%), medical oncologists (53.8%) and working in an academic setting (86.1%).

As compared to physicians attending the BCY3 conference, respondents of the BCC 2017 conference tended to be older ( $p=0.01$ ), with a higher number of male respondents ( $p=0.006$ ) from America ( $p=0.004$ ; Appendix Table A1).

Among the respondents, 101 (37.0%), 128 (46.9%), and 95 (34.8%) reported never having consulted the available international guidelines on fertility preservation, pregnancy in breast cancer survivors, and management of BCP, respectively (Figure 1; Appendix Table A2).

### Fertility preservation

The majority of the respondents (250, 91.6%) reported to usually or always discuss the risk of treatment-induced POI and infertility with their patients. However, between 17.6% and 48.3% of them believed to have inadequate knowledge about the 4 different strategies available for breast cancer patients to counteract the development of these side effects (Figure 2A; Appendix Table A3). For the respondents, the main factors preventing the access to these procedures were: patient-related factors (including age, social status, instruction, availability of a partner, prior children, cancer prognosis etc) in 147 (53.8%), cost of the strategies in 86 (31.5%), lack of collaboration with a specialized fertility center in 77 (28.2%), resistance of the medical team to potentially delay chemotherapy in 57 (20.9%), poor knowledge about these techniques in 49 (17.9%), resistance of the medical team to allow pregnancy after breast cancer in 34 (12.5%) or to the use of COS in 20 (7.3%).

As compared to physicians attending the BCY3 conference, a lower number of respondents of the BCC 2017 conference (8.3% vs. 19.0%;  $p=0.009$ ) considered resistance of the medical team to allow pregnancy after breast cancer as one of the factors preventing the access to these procedures (Appendix Table A3).

Up to 18.3% of respondents did not know if the different fertility preservation options were available in their country (Figure 2B; Appendix Table A4). As compared to physicians attending the BCY3 conference, a particularly low rate of availability for embryo cryopreservation was reported by the respondents of the BCC 2017 conference (27.4% vs. 43.8%;  $p=0.03$ ; Appendix Table A4). Embryo cryopreservation was the least commonly suggested strategy for fertility preservation (60.8%); temporary ovarian suppression with gonadotropin-releasing hormone analogs (GnRHa) during chemotherapy was the most commonly suggested option (81.0%; Figure 2C).

With the only exception of oocyte cryopreservation ( $p=0.003$ ), there was no difference in the attitudes towards the different strategies between the BCY3 and the BCC 2017 participants (Appendix Table A4).

Physicians' knowledge, attitudes and practice towards different aspects of fertility preservation in breast cancer patients are reported in Table 2.

A total of 118 (43.2%) respondents disagreed or were neutral on the statement that controlled ovarian stimulation (COS) can be considered safe in breast cancer patients; sixty-one (22.3%) and 48 (17.6%) suggested that COS should not be considered safe in patients with hormone receptor-positive disease and in those receiving neoadjuvant chemotherapy, respectively. Fifty-two (19.0%) responded that temporary ovarian suppression with GnRHa during chemotherapy should be proposed only to patients who cannot access other fertility preservation strategies.

As compared to physicians attending the BCY3 conference, a higher number of respondents of the BCC 2017 conference was neutral on the statement that ovarian tissue cryopreservation should be performed only in centers with adequate expertise (11.3% vs. 3.8%;  $p=0.03$ ; Appendix Table A5).

### Pregnancy after breast cancer

In breast cancer patients wishing to have a pregnancy after treatment, 94 (34.3%) respondents usually or always modify the proposed (neo)adjuvant systemic treatment in order to reduce the potential risk of POI and infertility (Figure 3; Appendix Table A6).

Physicians' knowledge, attitudes and practice towards different aspects of managing young breast cancer patients wishing to have a pregnancy after treatment are reported in Table 3.

Eighty-three (30.4%) and 101 (37.0%) respondents agreed or were neutral on the statements that a pregnancy in breast cancer survivors may increase the risk of recurrence overall or only in those with hormone receptor-positive disease, respectively. In contrast, 138 (50.5%) respondents agreed that a temporary interruption of endocrine therapy to allow pregnancy and 157 (57.5%) agreed that COS in breast cancer survivors can be safely considered.

As compared to physicians attending the BCY3 conference, a higher number of respondents of the BCC 2017 conference agreed that a pregnancy in breast cancer survivors may increase the risk of recurrence only in patients with hormone receptor-positive disease (15.5% vs. 5.7%;  $p=0.04$ ; Appendix Table A7).

### Breast cancer during pregnancy

Physicians' knowledge, attitudes and practice towards different aspects of managing BCP are reported in Table 3.

Seventy-one (26.0%) respondents believed that preterm delivery is the preferred option for patients diagnosed at the beginning of 3<sup>rd</sup> trimester of pregnancy in order to start chemotherapy in the post-partum period. Sixty-five (23.8%) and 104 (38.1%) disagreed or were neutral on the statement that endocrine therapy and anti-HER2 agents should be avoided

during pregnancy, respectively. A total of 133 (48.7%) respondents believed that the risk of abortion/fetal malformation in patients who become accidentally pregnant during trastuzumab is significant.

As compared to physicians attending the BCY3 conference, a higher number of respondents of the BCC 2017 conference disagreed on the statement that anti-HER2 therapy should be avoided in pregnant patients (16.7% vs. 4.8%;  $p=0.008$ ; Appendix Table A8).

## **Discussion**

This was a survey investigating knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients among physicians who attended the BCY3 and BCC 2017 conferences. Although the survey showed globally a positive and encouraging picture, we observed that adherence to guidelines on fertility preservation and management of pregnancy-related issues in young women with breast cancer remains sub-optimal even in this selected group of physicians with particular interest in breast cancer care.

Our survey differs from prior questionnaires [10–12] including recent ones [7,8] for several aspects that should be considered in the interpretation of the results. We aimed not to restrict the survey to a single nation or to oncologists only. Participants to this survey were expected to have higher than average interest in the management of women with breast cancer (and therefore, knowledge on these issues and willingness to discuss them as part of their clinical practice) as evidenced by their planned participation in these conferences, with an even higher specific expertise in the care of young patients for those who attended the BCY3 conference. Nevertheless, more than one of three responding physicians has never consulted the available guidelines on these topics and a non-negligible proportion of them did not seem to optimally address these issues with their young patients.

Current guidelines recommend discussing the possible risk of treatment-induced POI and infertility as well as the available options for fertility preservation with all newly diagnosed young cancer patients before starting anticancer treatment [2,5,6]. Despite more than 90% of the respondents reported to have this discussion with their young patients, we observed a non-optimal management of these issues in a significant proportion of them.

Embryo and oocyte cryopreservation are recommended as the first options to be discussed with young women interested in fertility preservation [2,5,6]. Nevertheless, up to almost half of the respondents admitted having inadequate knowledge on these strategies and one out of three responded that these options were not available in their countries or were not aware about their availability; this resulted in only 39.2% and 63.4% suggesting the use of embryo and oocyte cryopreservation to their patients, respectively. Despite several research efforts have been performed in this field over the past years, data on both the efficacy [13,14] and safety [15–17] of these strategies in breast cancer patients remain limited as compared to those in infertile non-oncologic women. This, together with the lack of adequate knowledge, probably explains the percentage ranging from 24.5% to 44.3% of neutral answers related to the statements investigating these strategies. For breast cancer patients, specific protocols for COS with the additional use of tamoxifen [18] or letrozole [13] are currently widely adopted and preferred for safety reasons [19] as also suggested by 40.3% of the respondents. However, to date, there is no evidence from randomized controlled trials that these protocols are superior and safer than standard protocols [20]. Results from the randomized STIM trial are awaited to address this important issue [21].

Ovarian tissue cryopreservation is still considered an experimental strategy for fertility preservation [2,5,6]; however, its success rates have reached promising levels over the past years [22]. Hence, this strategy can be also proposed to selected breast cancer patients such as

those with contraindication to COS [19]. Indeed, although for 45.1% of the respondents the knowledge on this strategy was considered inadequate and 27.8% reported that ovarian tissue cryopreservation was not available in their countries or did not know about its availability, 39.9% of them suggested its use in some circumstances. As reported by 90.1% of the respondents, ovarian tissue cryopreservation should be performed in centers with the adequate expertise [23–25]. As proposed by some authors [19], a possibility to optimize the procedure is to perform locally the harvesting of the tissue and to centralize the subsequent sample freezing and storage, a solution that was accepted by approximately 40% of the respondents.

Temporary ovarian suppression with GnRHa during chemotherapy was the most known (82.4%) as well as the most commonly suggested strategy (81.0%); a total 74.0% of the respondents reported that this option was covered by their national health systems. Indeed, in the last few years, the largest randomized controlled trials investigating the efficacy and safety of this procedure have reported positive results for both patients with hormone receptor-positive and negative breast cancer [26–28]; these findings were then further confirmed by recent meta-analyses [29,30]. Hence, temporary ovarian suppression with GnRHa during chemotherapy is now considered as an available option to be discussed with young breast cancer patients [2,31]. However, it should be highlighted that while the data are consistent on the efficacy of this strategy in reducing the risk of chemotherapy-induced POI, the number of post-treatment pregnancies described in these studies remains limited [29,30]. Hence, for patients interested in fertility preservation, temporary ovarian suppression with GnRHa during chemotherapy is not to be considered an alternative to cryopreservation strategies and is not mutually exclusive with them as incorrectly suggested by 19.0% of the respondents.



The completion of a family planning after treatment is an issue of great importance for a considerable proportion of young breast cancer patients [32]. However, many physicians and patients remain concerned about the safety of having a pregnancy in patients with prior history of breast cancer being a hormonally-driven form of tumor [7,33]. In our selected group of surveyed physicians, these concerns were confirmed: a total of 30.4% and 37.0% of the respondents agreed or were neutral on the statements that a pregnancy in breast cancer survivors may increase the risk of recurrence overall or only in those with hormone receptor-positive disease, respectively. However, this is not in line with the recent available data [34–36] supporting the statement that after adequate treatment and follow-up having a pregnancy can be considered safe including among patients with hormone receptor-positive tumors. The best timing (if any) for trying to have a pregnancy remains controversial with experts that suggest avoiding conception in the first 2 years following diagnosis [37]. This is an issue of great importance particularly among women with hormone receptor-positive disease that are candidates to receive up to 10 years of adjuvant endocrine therapy. In these patients, although 50.5% of the respondents believed that a temporary interruption of endocrine therapy to allow pregnancy could be considered safe, there are no data to support such a statement. The results of the ongoing POSITIVE trial investigating the safety of this approach are awaited to address this important unmet medical need [38].

For young breast cancer survivors requiring the use of assisted reproductive technology (ART), paucity of data are available to counsel them about the safety of its use [39]. However, more than half of the respondents agreed that ART including the use of COS could be considered safe in this setting. More data are needed on this regard; notably, the POSITIVE trial allows the use of ART in this setting and is awaited to provide important insights on this regard.

The last decade has witnessed important advances in the management of patients with BCP [4,5].

The surgical approach should not differ from the one in non-pregnant breast cancer patients and can be performed throughout the pregnancy period [4,5]. Although 18.3% of the respondents considered as not possible the use of sentinel lymph-node biopsy in these patients, recent data support the feasibility of this approach also in patients with BCP [40]. This is also endorsed by some of the available guidelines [4].

On the contrary, radiotherapy should be avoided during pregnancy [4,5], as correctly suggested by the majority (76.6%) of the respondents.

While the use of chemotherapy during the first trimester of pregnancy is associated with a high risk of abortion or fetal malformation, it can be administered in the second and third trimesters [4,5] as also confirmed by most (78.4%) of the respondents. As shown by Amant and colleagues, prematurity and not the use of chemotherapy is the main risk factor for paediatric development problems in children with prior in utero exposure to anticancer treatment [41]. Hence, although 26.0% of the respondents believe that preterm delivery is the preferred option in patients with BCP diagnosed in the early third trimester, the use of chemotherapy should be preferred in these cases to avoid prematurity [41]. Both the use of anthracycline-based regimens and taxanes during pregnancy are supported by current guidelines [4,5]; however, 33.3% and 27.8% of the respondents was against or neutral about the use of taxanes, respectively. The more limited evidence on the safety of administering taxanes during pregnancy [42,43] may be a possible explanation for these findings. Notably, although the use of chemotherapy can be considered safe during the second and third trimesters, its administration may increase the risk of complications such as small for gestational age and admission to the neonatal intensive care unit [44]. Therefore, as suggested

by almost 90% of the respondents, patients with BCP should be managed in centers with the adequate expertise [4,5].

Targeted treatments including both endocrine therapy and anti-HER2 agents should be avoided during pregnancy [4,5] as correctly stated by most of the respondents (76.2% and 61.9%, respectively). Nevertheless, unlike chemotherapy, there is no evidence that an accidental exposure to trastuzumab during the first trimester is associated with an increased risk of congenital malformations upon treatment discontinuation [45] as stated by almost half (48.7%) of the respondents. However, data are limited and no strong conclusions can be made.

A few drawbacks should be considered in the interpretation of our results. While the response rate was rather high for the BCY3 conference, only a minority of the participants to the BCC 2017 congress completed the survey. We had an overrepresentation of medical oncologists, from Western Europe and working in an academic setting; furthermore, given the target population, our findings refer specifically to physicians with particular interest in the management of breast cancer patients. Hence, these results cannot be extrapolated to the general community of physicians involved in cancer care and no information on the views of nursing staff, patients or caregivers was collected. Nevertheless, our survey was specifically designed to provide a representative picture of the status quo of the knowledge, attitudes and practice of this selected population of physicians towards fertility and pregnancy-related issues in young breast cancer patients. Moreover, with this specific design, we were able to capture the true response rate thus allowing to have a clearer idea on the potential impact of self-selection bias or sampling bias. Hence, we believe that our survey could serve as an important resource to understand the challenges and the needs for further training and information in this field.

In conclusion, our BCY3/BCC 2017 survey explored the current knowledge, attitudes and practice of physicians with specific interest in the management of young women with breast cancer towards the fertility and pregnancy-related issues faced by these patients. Although the survey showed globally a positive and encouraging picture, we observed the need for more educational initiatives and distribution of information even for this selected group of physicians to further improve their adherence to the available guidelines on fertility preservation and management of pregnancy-related issues in young breast cancer patients.

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### **Conflicts of interest**

Matteo Lambertini served as a consultant for Teva and received travel grants from Astellas outside the submitted work. Lucia Del Mastro received personal fees from Novartis Pharma AG, Roche-Genentech, Ipsen, Astrazeneca, Takeda, Eli Lilly 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 have declared no conflicts of interest.

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