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Original article

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

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ABSTRACT

Background: Fertility and pregnancy-related issues are major concerns for young breast cancer patients. Limited data are available on physicians' knowledge, attitudes and practice in these fields.
Methods: A 26-item questionnaire exploring 3 different topics (fertility preservation, pregnancy after breast cancer and breast cancer during pregnancy) was sent by email to physicians attending the 2016 3rd European School of Oncology (ESO) – European Society for Medical Oncology (ESMO) Breast Cancer in Young Women Conference (BCY3) and the 15th St. Gallen International Breast Cancer Conference 2017 (BCC 2017). Given the selected sample, survey respondents were expected to have a higher than average interest in the management of breast cancer patients. Descriptive analyses were performed.
Results: A total of 273 physicians (105 at BCY3 and 168 at BCC 2017) completed the survey; 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 breast cancer during pregnancy, respectively. Up to 18.3% of respondents did not know if the different fertility preservation options were available in their country; 22.3% suggested that controlled ovarian stimulation should not be considered safe in patients with hormone receptor-positive disease. A total of 30.4% of respondents agreed or were neutral on the statement that pregnancy in breast cancer survivors may increase the risk of recurrence. Regarding breast cancer during pregnancy, 23.8% and 38.1% disagreed or were neutral on the statements that endocrine therapy and anti-HER2 agents should be avoided during pregnancy, respectively.
Conclusions: Further educational initiatives are needed to improve physicians' knowledge and adherence to available guidelines when addressing fertility and pregnancy-related issues in young breast cancer patients.

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1. 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 premature ovarian insufficiency and infertility [3]. This is of major concern given the current trend of postponing pregnancy to later in life; as a consequence, an increasing proportion of young women with breast cancer is diagnosed before completing their family plans [2]. In addition, an increased awareness should be paid to breast cancer during pregnancy whose occurrence also increases with age [4].

Over the past years, solid evidence has been accumulated to support the management of young patients facing fertility and pregnancy-related issues [3]. Specific international guidelines have been developed to help physicians in dealing with fertility preservation in cancer patients [5,6], pregnancy following anticancer treatments [5], and management of women diagnosed with breast cancer during pregnancy [4,5]. However, several controversies remain in these fields and some physicians are still uncomfortable dealing with these issues [7,8].

To further explore the current knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young breast cancer patients, we conducted 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 focusing on physicians with specific interest in the management of breast cancer patients and exploring three topics: fertility preservation, pregnancy after breast cancer and breast cancer during pregnancy.

2. Materials and methods

A specifically developed questionnaire (Supplementary Appendix 1) investigating fertility and pregnancy-related issues was given to physicians attending the 2016 3rd European School of Oncology (ESO) – European Society for Medical Oncology (ESMO) Breast Cancer in Young Women Conference (BCY3) held in Lugano (Switzerland) on November 10–12, 2016 [2], and the 15th 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 and advocates involved in the management of breast cancer patients participated in these conferences.

The final survey was distributed electronically in advance to all participants attending the BCY3 and BCC 2017 conferences. After accessing the online platform, only physicians were allowed to enter and 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.

2.1. Characteristics of the survey

The 26-item survey was divided in 4 main sections: 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 breast cancer during pregnancy.

The questionnaire was developed on the basis of prior surveys on these topics conducted both in Europe and the United States [10–12] and adapted to the BCY3/BCC 2017 context. 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 knowledge of physicians towards these topics was investigated either by using a four-point Likert scale (from “not at all knowledgeable” to “very knowledgeable”) or, in controversial items, by using a five-point Likert scale (from “strongly disagree” to “strongly agree”).

Table 1
Demographic, medical training and background information of the responding physicians (N = 273).

	Responding physicians (N = 273)
Age, median (interquartile)	46 (38–55)
Age category	
<40	79 (28.9)
40-50	93 (34.1)
>50	96 (35.2)
Missing	5 (1.8)
Gender	
Female	156 (57.1)
Male	117 (42.9)
Region of practice	
Western Europe	154 (56.4)
Eastern Europe	29 (10.6)
America	36 (13.2)
Asia	35 (12.8)
Africa	10 (3.7)
Oceania	5 (1.8)
Missing	4 (1.5)
Religion	
Catholic	114 (41.8)
Protestant	34 (12.4)
Muslim	18 (6.6)
Jewish	12 (4.4)
Hindu	6 (2.2)
Atheist/none	61 (22.3)
Prefer not to answer	28 (10.3)
Children	
Yes	213 (78.0)
No	60 (22.0)
Specialty	
Medical oncology	147 (53.8)
Surgery	82 (30.0)
Gynaecology	26 (9.5)
Family physician	2 (0.7)
Fertility specialist	1 (0.4)
Other[a]	15 (5.5)
Practice environment	
Public	14 (5.1)
Private	24 (8.8)
Academic	235 (86.1)
Years of clinical practice, median (interquartile)	18 (10–26)
Work in breast cancer unit	
Yes	223 (81.7)
No	50 (18.3)
New young breast cancer patients (≤40 years) every year	
<10	47 (17.2)
10-50	173 (63.4)
>50	53 (19.4)
Patients with breast cancer treated during pregnancy every year	
0	51 (18.7)
1-5	188 (68.9)
6-10	32 (11.7)
>10	2 (0.7)

[a] Radiology, radiation oncology.

2.2. Study objectives

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

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.

2.3. 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 or 150 respondents would allow a margin of error in the estimate of the proportion of approximately ±8% or ±5.67%, respectively, 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 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, given the potentially different professional profile of physicians attending the two events. The levels of evidence and grades of recommendation reported in the Tables were based on the scoring system used in the ESMO guidelines on cancer, pregnancy and fertility (Supplementary Appendix 2, Table A1) [5].

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.

3. Results

Out of 275 participants attending the BCY3 conference, 124 (45.1%) accessed the survey: 19 of them were not physicians leaving a total of 105 eligible completed questionnaires. Among approximately 3000 participants at the BCC 2017 conference, 210 (7.0%) accessed the survey: 20 of them were not physicians and 22 had already completed the survey at the time of the BCY3 conference leaving a total of 168 eligible completed questionnaires. Hence, the main analyses were performed on 273 responding physicians.

Median age of the respondents was 46 years (interquartile range 38–55); the majority were female (57.1%), from Western Europe (56.4%), medical oncologists (53.8%) and working in an academic setting (86.1%; Table 1). As compared to physicians attending the BCY3 conference, BCC 2017 respondents tended to be older ($p = 0.01$), with a higher number of male respondents ($p = 0.006$) from America ($p = 0.004$; Supplementary Appendix 2, Table A2).

A total of 101 (37.0%), 128 (46.9%), and 95 (34.8%) respondents reported never having consulted the available international guidelines on fertility preservation, pregnancy in breast cancer survivors, and management of breast cancer during pregnancy, respectively (Fig. 1; Supplementary Appendix 2, Table A3). Among them, 33 (12.1%), 39 (14.3%), and 23 (8.4%) were not aware about the existence of these guidelines, respectively (Fig. 1; Supplementary Appendix 2, Table A3).

3.1. Fertility preservation

The majority of the respondents ($n = 250$, 91.6%) reported to usually or always discuss the risk of treatment-induced premature ovarian insufficiency and infertility with their patients. However, between 17.6% and 48.4% of them believed to have inadequate knowledge about the 4 different strategies (embryo cryopreservation, oocyte cryopreservation, ovarian tissue cryopreservation, and temporary ovarian suppression with gonadotropin-releasing

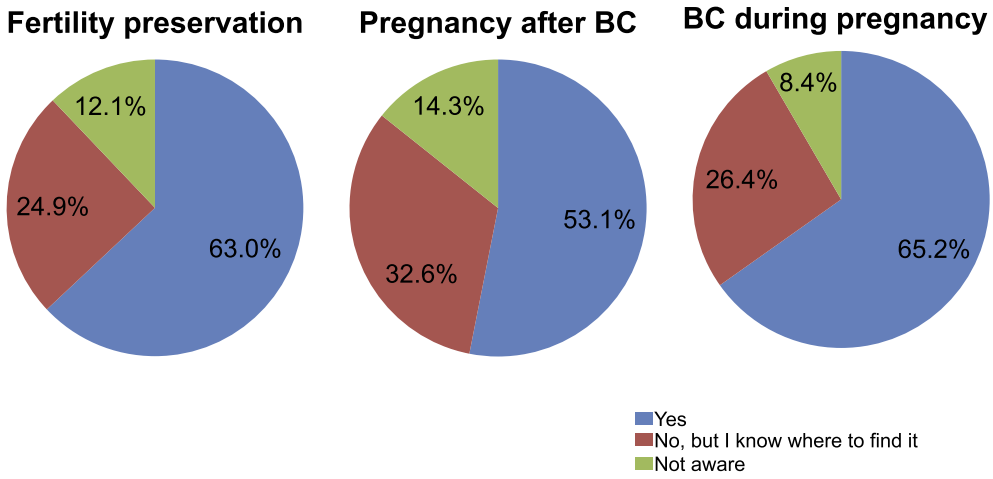

Fig. 1. Physicians' knowledge on the available international guidelines on fertility preservation, pregnancy in breast cancer survivors, and management of breast cancer during pregnancy. BC, breast cancer.

hormone agonists [GnRHa] during chemotherapy) available for breast cancer patients to counteract the development of these side effects (Fig. 2A; Supplementary Appendix 2, Table A4). The main factors preventing access to these procedures were: patient-related factors (including age, social status, education, availability of a partner, prior children, cancer prognosis etc; n = 147, 53.8%), cost of the strategies (n = 86, 31.5%), lack of collaboration with a specialized fertility centre (n = 77, 28.2%), resistance of the medical team to potentially delay chemotherapy (n = 57, 20.9%), poor knowledge about these techniques (n = 49, 17.9%), resistance of the medical team to allow pregnancy after breast cancer (n = 34, 12.5%) or to use controlled ovarian stimulation (n = 20, 7.3%).

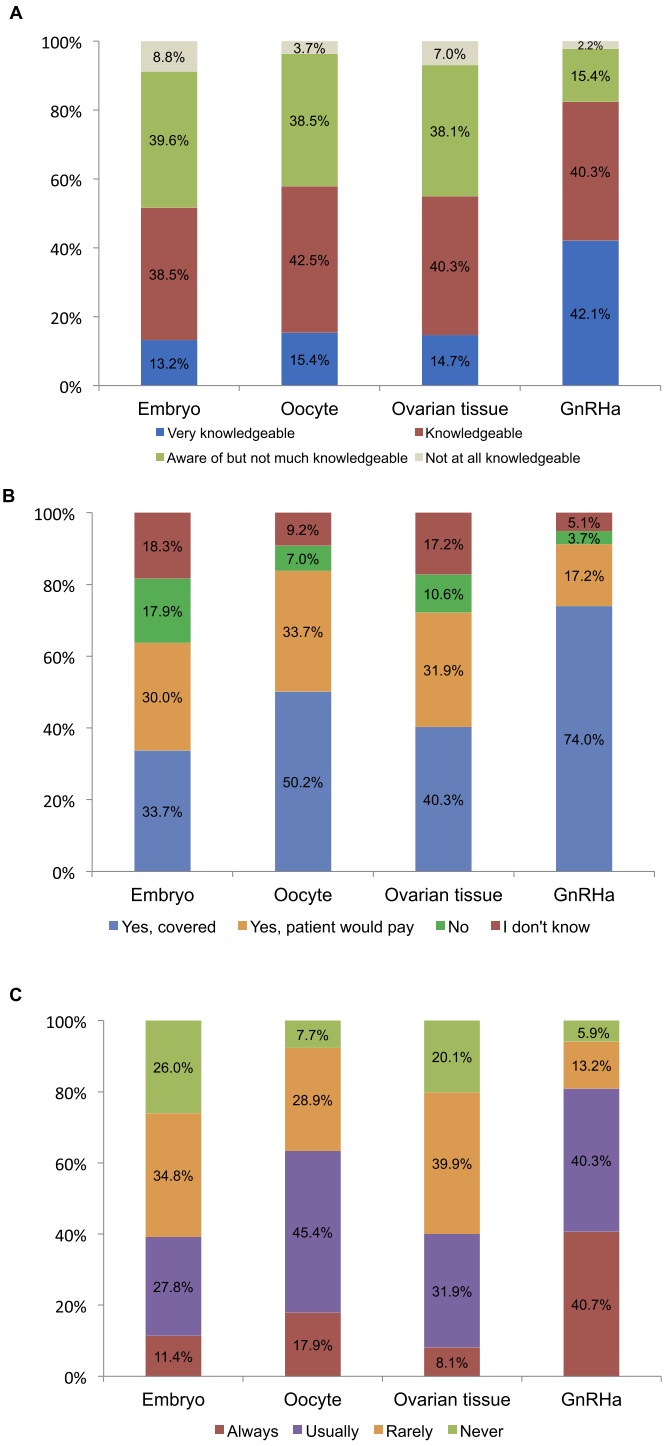

Fig. 2. Strategies for fertility preservation in breast cancer patients: A) Physicians' knowledge; B) Availability; C) Prescription. GnRHa, gonadotropin-releasing hormone agonists.

Between 5.1% and 18.3% of respondents did not know if the different fertility preservation options were available in their country (Fig. 2B; Supplementary Appendix 2, Table A5). Embryo cryopreservation was the least commonly suggested strategy for fertility preservation (39.2%), while temporary ovarian suppression with GnRHa during chemotherapy the most commonly suggested (81.0%; Fig. 2C).

Physicians' knowledge, attitudes and practice towards specific aspects of fertility preservation in breast cancer patients are reported in Table 2 and Supplementary Appendix 2, Table A6.

A total of 118 (43.2%) respondents disagreed or were neutral on the statement that controlled ovarian stimulation can be considered safe in breast cancer patients; sixty-one (22.3%) and 48 (17.6%) suggested that controlled ovarian stimulation 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.

3.2. Pregnancy after breast cancer

In breast cancer patients wishing to conceive after treatment, 94 (34.4%) respondents usually or always modify the proposed (neo) adjuvant systemic treatment in order to reduce the potential risk of premature ovarian insufficiency and infertility (Supplementary Appendix 2, Fig. A1; Supplementary Appendix 2, Table A7).

Physicians' knowledge, attitudes and practice towards different aspects of managing young breast cancer patients with pregnancy desire are reported in Table 3 and Supplementary Appendix 2, Table A8.

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 either 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%) that controlled ovarian stimulation in breast cancer survivors can be safely considered.

3.3. Breast cancer during pregnancy

Physicians' knowledge, attitudes and practice towards different aspects of managing breast cancer during pregnancy are reported in Table 4 and Supplementary Appendix 2, Table A9.

Seventy-one (26.0%) respondents believed that preterm delivery is the preferred option for patients diagnosed at the beginning of 3rd 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.

4. Discussion

This survey investigated 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 globally showed a positive and

Table 2
Physicians' knowledge, attitudes and practice towards fertility preservation in breast cancer patients (N = 273).

	Agree	Neutral	Disagree
A centre for assisted reproductive techniques is needed within the same oncology unit	164 (60.1)	54 (19.8)	55 (20.1)
Experts recommend having a well-organized interaction between oncology and fertility units even not necessarily within the same institutions [19]. Level of Evidence[a]: V, C			
Controlled ovarian simulation should be considered safe in all patients	155 (56.8)	67 (24.5)	51 (18.7)
No negative impact on patients' outcomes was shown for breast cancer patients who underwent controlled ovarian stimulation (with a protocol that included letrozole) before starting chemotherapy [15]. Level of Evidence[a]: III, B			
Controlled ovarian simulation should not be considered safe in women with hormone receptor-positive breast cancer	61 (22.3)	80 (29.3)	132 (48.4)
No negative impact on patients' outcomes was shown for breast cancer patients who underwent controlled ovarian stimulation (with a protocol that included letrozole) before starting chemotherapy irrespective of the hormone receptor status of the tumor [15]. Level of Evidence[a]: III, C			
Controlled ovarian simulation should not be considered safe in patients who are candidates to neoadjuvant chemotherapy	48 (17.6)	73 (26.7)	152 (55.7)
No negative impact on patients' outcomes was shown for breast cancer patients who underwent controlled ovarian stimulation (with a protocol that included letrozole) before starting chemotherapy irrespective of the timing for surgery [15]. Level of Evidence[a]: III, C			
Protocols for controlled ovarian stimulation in breast cancer patients should include letrozole or tamoxifene	110 (40.3)	121 (44.3)	42 (15.4)
The limited available safety data with controlled ovarian stimulation in breast cancer patients are with a protocol that included letrozole [15]. Level of Evidence[a]: III, B			
Likelihood of pregnancy with cryopreservation strategies in cancer patients is comparable to the non-oncologic infertile population	100 (36.6)	97 (35.5)	76 (27.8)
The limited available efficacy data in cancer patients showed no difference in pregnancy rates as compared to the non-oncologic population [13]. Level of Evidence[a]: III, B			
Ovarian tissue cryopreservation should be performed only in centres with adequate expertise	246 (90.1)	23 (8.4)	4 (1.5)
Due to the impact on the efficacy of the technique, ovarian tissue cryopreservation should be performed in centres with the adequate expertise [23–25]. Level of Evidence[a]: IV, B			
Harvesting of the cryopreserved ovarian tissue can be performed locally, and then sample freezing and storage can be centralized	109 (39.9)	120 (44.0)	44 (16.1)
In order to optimize the procedure in terms of both patient management and cost-effectiveness, experts recommend performing the harvesting of the tissue locally and the subsequent sample freezing and storage centrally [19]. Level of Evidence[a]: V, C			
Ovarian suppression with GnRHa during chemotherapy should be proposed only to patients who cannot access other cryopreservation techniques	52 (19.0)	70 (25.6)	151 (55.3)
Ovarian suppression with GnRHa during chemotherapy can be proposed to patients interested in ovarian function preservation (irrespectively of their interest in fertility preservation) as well as in women interested in fertility preservation after cryopreservation strategies or in those who cannot access cryopreservation techniques [30]. Level of Evidence[a]: I, B			
Ovarian suppression with GnRHa during chemotherapy should be proposed only to women with hormone receptor-negative breast cancer	39 (14.3)	58 (21.2)	176 (64.5)
Ovarian suppression with GnRHa during chemotherapy showed to be effective and safe in both patients with hormone receptor-positive and negative breast cancer; therefore, it can be proposed to all breast cancer patients irrespectively of the hormone receptor status of their tumor [30]. Level of Evidence[a]: I, B			

[a] Defined as in the ESMO guidelines (Supplementary Appendix 2, Table A1) [5] GnRHa, gonadotropin-releasing hormone agonists.

encouraging picture, 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 interpreting the results. We aimed not to restrict the survey to a single nation or to oncologists only. Participants were expected to have higher than average interest in the management of women with breast cancer (and therefore, broader knowledge on these issues and willingness to discuss them as part of their clinical practice) as inferred by their participation in these dedicated conferences, with an even higher specific expertise in the care of young patients for those who attended the BCY3 conference. Nevertheless, more than one third of the responding physicians have 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 premature ovarian insufficiency and infertility as well as the available options for fertility preservation with all newly diagnosed young cancer patients before starting anticancer treatments [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 by many 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]. Nonetheless, up to almost half of the respondents admitted having inadequate knowledge on these strategies and one out of three responded that these options were either not available in their countries or they were not aware about their availability; this resulted in only 39.2% and 63.3% 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 controlled ovarian stimulation 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 (NTR4108) 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].

Table 3
Physicians' knowledge, attitudes and practice towards pregnancy after breast cancer (N = 273).

	Agree	Neutral	Disagree
Abortion in breast cancer survivors is therapeutic and should be considered	11 (4.0)	22 (8.1)	240 (87.9)
Abortion did not appear to impact on patients' outcomes; therefore, it should not be promoted for therapeutic reasons [38]. Level of Evidence[a]: IV, C			
A pregnancy in breast cancer survivors may increase the risk of recurrence	34 (12.5)	49 (17.9)	190 (69.6)
Having a pregnancy after prior history of breast cancer did not appear to negatively impact on patients' outcomes [36–38]. Level of Evidence[a]: IV, B			
A pregnancy in breast cancer survivors within 2 years from diagnosis may increase the risk of recurrence	61 (22.3)	74 (27.1)	138 (50.5)
The interval between diagnosis and pregnancy did not appear to impact on patients' outcomes [38]. Level of Evidence[a]: IV, C			
A pregnancy in breast cancer survivors may increase the risk of recurrence only in women with hormone receptor-positive disease	32 (11.7)	69 (25.3)	172 (63.0)
Having a pregnancy after prior history of hormone receptor-positive breast cancer did not appear to negatively impact on patients' outcomes [38]. Level of Evidence[a]: IV, B			
A temporary interruption of endocrine therapy to allow pregnancy in women with hormone receptor-positive disease can be considered safe	138 (50.5)	88 (32.2)	47 (17.2)
No data are available so far to counsel patients on this regard; the ongoing POSITIVE trial (IBCSG 48-14 NCT02308085) is investigating this issue [40].			
A pregnancy in breast cancer survivors should be managed as "high risk" pregnancy	143 (52.4)	69 (25.3)	61 (22.3)
A higher risk of pregnancy complications in breast cancer survivors has been observed suggesting the need of a closer follow-up for these pregnancies [36–38]. Level of Evidence[a]: IV, B			
Breastfeeding in breast cancer survivors is safe and can be encouraged	209 (76.6)	49 (17.9)	15 (5.5)
Breastfeeding in breast cancer survivors showed to be feasible and did not appear to impact on patients' outcomes [38]. Level of Evidence[a]: IV, C			
Assisted reproductive techniques can be safely performed also in breast cancer survivors	163 (59.7)	80 (29.3)	30 (11.0)
Despite the limited available data, the use of assisted reproductive techniques in breast cancer survivors showed to be feasible and did not appear to impact on patients' outcomes [41]. Level of Evidence[a]: V, C			
Controlled ovarian stimulation can be safely performed also in breast cancer survivors	157 (57.5)	80 (29.3)	36 (13.2)
Despite the limited available data, the use of controlled ovarian stimulation in breast cancer survivors showed to be feasible and did not appear to impact on patients' outcomes [41]. Level of Evidence[a]: V, C			
Egg donation can be safely performed also in breast cancer survivors	141 (51.6)	104 (38.1)	28 (10.3)
Despite the limited available data, the use of egg donation in breast cancer survivors showed to be feasible and did not appear to impact on patients' outcomes [41]. Level of Evidence[a]: V, C			
Transplantation of cryopreserved ovarian tissue harvested at the time of cancer diagnosis can be safely performed in breast cancer survivors to restore fertility	174 (63.7)	91 (33.3)	8 (2.9)
Although ovarian tissue cryopreservation and subsequent transplantation is still considered an experimental technique, it can be used in some breast cancer patients (such as women with contraindication to controlled ovarian stimulation or in need to start quickly neoadjuvant chemotherapy) [22]. Level of Evidence[a]: IV, B			

[a] Defined as in the ESMO guidelines (Supplementary Appendix 2, Table A1) [5].

Hence, this strategy can also be proposed to selected breast cancer patients such as those with contraindication to controlled ovarian stimulation or in need to start quickly neoadjuvant chemotherapy [19]. Indeed, although for 45.1% of the respondents the knowledge on this strategy was considered inadequate and 27.8% reported that it was not available in their countries or did not know about its availability, 40.0% of them suggested its use in some circumstances. As reported by 90.1% of the respondents, ovarian tissue cryopreservation should be performed in centres 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 39.9% of the respondents.

Temporary ovarian suppression with GnRHa during chemotherapy was the most known (82.4%) and commonly suggested strategy (81.0%), covered by their national health systems or institutions for 74.0% of the respondents. 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 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 despite consistent data on the efficacy of this strategy in reducing the risk of chemotherapy-induced premature ovarian insufficiency, 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 these methods are not mutually exclusive 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 [32–34]. However, many physicians and patients remain concerned about the safety of conceiving after breast cancer being a hormonally-driven tumor [7,35]. 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 either overall or only in those with hormone receptor-positive disease, respectively. However, this belief is not in line with the recent available data [36–38] suggesting the safety of having a pregnancy also in patients with hormone receptor-positive tumors [38] after adequate treatment and follow-up. The best timing (if any) for trying to conceive remains controversial with experts suggesting avoiding conception within 2 years after diagnosis [39]. This is an issue of great importance particularly among women with hormone receptor-positive disease candidates to receive up to 10 years of adjuvant endocrine therapy. A total of 50.5% of the respondents believed that a temporary interruption of endocrine therapy to allow pregnancy could be considered safe: however, the results of the ongoing POSITIVE trial (IBCSG 48-14 NCT02308085) investigating the safety of this approach are awaited to answer this important unmet medical question [40].

Paucity of data are available to counsel young breast cancer survivors about the safety of assisted reproductive technology (ART) [41]. However, more than half of the respondents agreed that ART, including the use of controlled ovarian stimulation, could be considered safe in this setting. More data are needed on this regard;

Table 4
Physicians' knowledge, attitudes and practice towards managing breast cancer during pregnancy (N = 273).

	Agree	Neutral	Disagree
Breast cancer during pregnancy should be managed in centres with adequate expertise	245(89.7)	16 (5.9)	12 (4.4)
Considering the need to involve a multidisciplinary team since the early phases, experts recommend to manage these patients in centres with the adequate expertise [5]. Level of Evidence[a]: V, B			
Breast cancer during pregnancy even when adequately treated is associated with worse prognosis	86 (31.5)	45 (16.5)	142 (52.0)
Differently from breast cancer diagnosed during the first year after delivery, the diagnosis of breast cancer during pregnancy does not seem to be an independent poor prognostic factor when standard treatment is administered [4]. Level of Evidence[a]: IV, B			
In breast cancer patients who need to start immediately chemotherapy and diagnosed in the 1st trimester, abortion is the preferred option	158 (57.9)	59 (21.6)	56 (20.5)
This is the only clinical situation for which abortion should be preferred [4,5]. Level of Evidence[a]: III, B			
In patients diagnosed in the early 3rd trimester of pregnancy, preterm delivery in order to start cancer treatment in the postpartum period is the preferred option	71 (26.0)	45 (16.5)	157(57.5)
Prematurity and not the use of chemotherapy appears to be the main risk factor for development problems in children with prior in utero exposure to anticancer treatments; therefore, the use of chemotherapy should be preferred in these cases to avoid prematurity [43]. Level of Evidence[a]: III, B			
In patients diagnosed in the early 3rd trimester of pregnancy, starting cancer treatment during pregnancy to have a delivery at term is the preferred option	183 (67.0)	57 (20.9)	33 (12.1)
Prematurity and not the use of chemotherapy appears to be the main risk factor for development problems in children with prior in utero exposure to anticancer treatments; therefore, the use of chemotherapy should be preferred in these cases to avoid prematurity [43]. Level of Evidence[a]: III, B			
Breast conserving surgery during pregnancy can be considered	208 (76.2)	32 (11.7)	33 (12.1)
The surgical approach should not differ from the one in non-pregnant breast cancer patients and can be performed throughout the entire pregnancy period [4,5]. Level of Evidence[a]: III, B			
Sentinel lymph-node biopsy during pregnancy can be considered	178 (65.2)	45 (16.5)	50 (18.3)
Sentinel lymph-node biopsy appeared to be feasible also in patients with breast cancer during pregnancy and may be considered [42]. Level of Evidence[a]: III, B			
Radiotherapy during pregnancy can be considered	24 (8.8)	40 (14.7)	209 (76.6)
Radiotherapy should be avoided during pregnancy [4,5]. Level of Evidence[a]: IV, B			
Chemotherapy can be safely administered during the 1st trimester of pregnancy	11 (4.0)	31 (11.4)	231 (84.6)
Considering the high risk of abortion or fetal malformation, the use of chemotherapy during the first trimester of pregnancy is contraindicated [43–46]. Level of Evidence[a]: III, B			
Chemotherapy can be safely administered during the 2nd/3rd trimester of pregnancy	214 (78.4)	32 (11.7)	27 (9.9)
Considering the safety available data, chemotherapy during the 2nd/3rd trimester of pregnancy can be considered [43–46]. Level of Evidence[a]: III, B			
Taxane-based chemotherapy should be avoided during pregnancy	91 (33.3)	76 (27.8)	106 (38.8)
Considering the safety available data although more limited than for anthracycline-based regimens, taxanes can be considered during the 2nd/3rd trimester of pregnancy [43–46]. Level of Evidence[a]: III, B			
Dose-dense chemotherapy should be avoided during pregnancy	131 (48.0)	96 (35.2)	46 (16.8)
Considering the higher risk of adverse events and the need for G-CSF use, dose-dense chemotherapy should be avoided during pregnancy [4,5]. Level of Evidence[a]: IV, B			
Endocrine therapy should be avoided during pregnancy	208 (76.2)	45 (16.5)	20 (7.3)
Endocrine therapy should be avoided during pregnancy [4,5]. Level of Evidence[a]: IV, B			
Anti-HER2 therapy should be avoided during pregnancy	169 (61.9)	71 (26.0)	33 (12.1)
Anti-HER2 therapy should be avoided during pregnancy [4,5]. Level of Evidence[a]: IV, B			
In patients who become accidentally pregnant during chemotherapy, there is a significant risk of abortion/fetal malformation	193 (70.7)	49 (17.9)	31 (11.4)
Exposure to chemotherapy during the first trimester of pregnancy is associated with a high risk of abortion or fetal malformation [43–46]. Level of Evidence[a]: III, B			
In patients who become accidentally pregnant during trastuzumab, there is a significant risk of abortion/fetal malformation	133 (48.7)	88 (32.2)	52 (19.0)
Although the data are limited on this regard, there is no evidence that exposure to trastuzumab during the first trimester of pregnancy is associated with a high risk of abortion or fetal malformation [47,48]. Level of Evidence[a]: IV, B			

[a] Defined as in the ESMO guidelines (Supplementary Appendix 2, Table A1) [5] G-CSG, granulocyte-colony stimulating factors.

notably, the POSITIVE trial allows the use of ART in this setting and may provide some insights on this regard.

The last decade has witnessed important advances in the management of patients with breast cancer during pregnancy [4,5].

The surgical approach should not differ from the one in non-pregnant breast cancer patients and can be performed throughout the entire pregnancy period [4,5]. Although 18.3% of the respondents considered not possible the use of sentinel lymph-node biopsy in these patients, recent data support the feasibility of this approach also in patients with breast cancer during pregnancy [42]. 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 2nd/3rd trimesters [4,5] as also confirmed by most (78.4%) of the respondents. Prematurity and not the use of chemotherapy appears to be the main risk factor for development problems in children with prior in utero exposure to anticancer treatments [43]. Hence, although 26.0% of the respondents believe that preterm delivery is the preferred option in patients with breast cancer during pregnancy diagnosed in the early 3rd trimester, the use of chemotherapy should be preferred in these cases to avoid prematurity [43]. 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 [44,45] may be a possible explanation for these findings. Notably, although the use of chemotherapy can be considered safe during the 2nd/3rd trimesters, its administration may increase the risk of complications such as small for gestational age and admission to the neonatal intensive care unit [46]. Therefore, as suggested by almost 90% of the respondents, patients with breast cancer during pregnancy

should be managed in centres 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 [47,48] as stated by almost half (48.7%) of the respondents. However, data are limited and no strong conclusions can be made on this issue.

A few drawbacks should be considered when interpreting our results. The wording of some statements with double negatives may have been difficult for responding physicians. While the response rate was relatively high for the BCY3 participants (45.1%), only a minority of the attendees of the BCC 2017 congress completed the survey (7.0%). 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. 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, although our BCY3/BCC 2017 survey showed globally a positive and encouraging picture, we register the clear need for more educational initiatives and distribution of information even among this highly 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 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.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.breast.2018.08.099.

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