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Knowledge, Practice, and Attitudes of Physicians in Low- and Middle-Income Countries on Fertility and Pregnancy-Related Issues in Young Women With Breast Cancer

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abstract

PURPOSE Fertility and pregnancy-related issues are highly relevant for young (≤ 40 years) patients with breast cancer. Limited evidence exists on knowledge, practice, and attitudes of physicians from low- and middle-income countries (LMICs) regarding these issues.

METHODS A 19-item questionnaire adapted from an international survey exploring issues about fertility preservation and pregnancy after breast cancer was sent by e-mail between November 2019 and January 2020 to physicians from LMICs involved in breast cancer care. Descriptive analyses were performed.

RESULTS A total of 288 physicians from Asia, Africa, America, and Europe completed the survey. Median age was 38 years. Responders were mainly medical oncologists (44.4%) working in an academic setting (46.9%). Among responders, 40.2% and 53.8% reported having never consulted the available international guidelines on fertility preservation and pregnancy after breast cancer, respectively. 25.0%, 19.1%, and 24.3% of responders answered to be not at all knowledgeable about embryo, oocyte, or ovarian tissue cryopreservation, respectively; 29.2%, 23.6%, and 31.3% declared that embryo, oocyte, and ovarian tissue cryopreservation were not available in their countries, respectively. 57.6% of responders disagreed or were neutral on the statement that controlled ovarian stimulation can be considered safe in patients with breast cancer. 49.7% and 58.6% of responders agreed or were neutral on the statement that pregnancy in breast cancer survivors may increase the risk of recurrence overall or only in those with hormone receptor–positive disease, respectively.

CONCLUSION This survey showed suboptimal knowledge, practice, and attitudes of physicians from LMICs on fertility preservation and pregnancy after treatment completion in young women with breast cancer. Increasing awareness and education on these aspects are needed to improve adherence to available guidelines and to promote patients' oncofertility counseling.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

In young women worldwide, breast cancer is the most common tumor accounting for more than 30% of the total cases of newly diagnosed malignancies in patients younger than 40 years.[1] Although breast cancer arising at a young age represents a minority of the total number of new diagnoses of breast malignancies in Western countries,[2] it has a more significant burden in low- and middle-income countries (LMICs).[3,4] The reasons behind these epidemiologic differences across countries are poorly understood but they may be related to different age distribution of the population, reproductive behaviors, overall life expectancy, competitive causes of death, and environmental and genetic risk factors.[5-7]

Breast cancer in young women is considered a public health problem because of its economic and societal implications, as well as the several age-related complex issues that need to be considered in the care of these patients.[8,9] Among them, the development of premature ovarian insufficiency (POI) and subsequent infertility as a consequence of the use of anticancer therapies deserves special attention.[10] Many young women are concerned about developing these side effects, and the desire for a future pregnancy may

CONTEXT

Key Objective

To explore knowledge, practice, and attitudes of physicians from low- and middle-income countries (LMICs) regarding fertility and pregnancy-related issues in young women with breast cancer.

Knowledge Generated

This survey provides an important picture of the current status on how fertility preservation and pregnancy after treatment completion in young women with breast cancer are managed by the 288 responding physicians practicing in LMICs from Asia, Africa, America, and Europe. We observed suboptimal adherence to guidelines when managing these issues that are of high relevance to many young patients.

Relevance

These results highlight the need for implementing targeted efforts in LMICs to overcome barriers and to increase awareness and education for improving adherence to available guidelines and patients' oncofertility counseling.

influence their treatment decisions.[11-14] Thus, performing adequate oncofertility counseling and offering the available strategies for fertility preservation to improve chances of conception following anticancer therapies is now considered a key component in the care of young women with cancer.[15-17]

Well-established models of care in oncofertility exist to help physicians in dealing with these issues.[18,19] However, knowledge, practice, and attitudes of breast cancer specialists toward management of fertility and pregnancy-related concerns in young patients are not always optimal.[20] In our prior survey, the majority of responders were from Western countries, with only a minority of responding physicians practicing in LMICs.[20] Considering that treating breast cancer in LMICs poses additional challenges including inequities in access to screening and effective therapeutic options,[21-23] it is of paramount importance to investigate potential disparities in survivorship care, particularly in the field of oncofertility, also considering the different reproductive behaviors and fertility-related challenges compared with Western countries.[24,25] Notably, lack of clear evidence exists on how survivorship care in young women with breast cancer is managed in LMICs.[26]

The present survey aimed at investigating knowledge, practice, and attitudes of physicians involved in cancer care and practicing in LMICs on fertility and pregnancy-related issues in young (≤ 40 years) women with breast cancer to portray treatment patterns and to raise awareness on the needs related to these important aspects of the care of these patients.

METHODS

An anonymous online survey was created by medical oncologists involved in breast cancer care. This survey was adapted from a prior questionnaire that was specifically created for the ESO-ESMO Breast Cancer in Young Women International Conference (BCY) by physicians from different specialties (medical oncologists, gynecologists, and fertility specialists) involved in the care of breast cancer in young women with a main expertise in the field of oncofertility.[20] Specifically, the present survey covered issues related to fertility preservation and pregnancy after treatment completion in young women with breast cancer.

Between November 2019 and January 2020, the questionnaire was e-mailed to physicians involved in the management of patients with breast cancer and practicing in LMICs (defined according to the World Bank income grouping).[27] In each country, a physician ambassador was selected and was responsible for local recruitment of physicians. The online platform for accessing the questionnaire was open for 60 days.

Institutional review board approval was not sought for this study following the Medical Research Council's advice that this work represented a low-risk health investigation, in alignment with the US 45 CFR 46 section 104 (category 5 for exemption). The research project was presented to study participants and they were asked for voluntary participation after provision of an informative letter for anonymized confidential data collection. Data processing complied with the EU General Data Protection Regulation (GDPR 2016/679) for information security.

Characteristics of the Survey

The survey included a 19-item structured questionnaire with multiple-choice mandatory answers divided into the following three sections (Data Supplement):

1. Demographic, medical training, and background information (questions 1-9)
2. Knowledge, practice, and attitudes of physicians toward fertility preservation in young women with breast cancer (questions 10-16)
3. Knowledge, practice, and attitudes of physicians toward pregnancy after breast cancer diagnosis and treatment (questions 17-19)

Knowledge, practice, and attitudes of physicians toward these topics were investigated either by using Likert scales (from not at all knowledgeable to very knowledgeable, from

never to always, and from disagree to agree), or by appositely created answer's options.

Statistical Analysis

Descriptive analyses were conducted. Characteristics of responding physicians were described as the absolute number of responders for each answer's option on the total number of people responding to the questionnaire. If more than one option was allowed, the sum of percentages for each answer's option is foreseeably different from 100%.

RESULTS

Demographic, Medical Training, and Background Information

A total of 288 physicians practicing in LMICs and involved in breast cancer management took part in the survey (Table 1).

Responding physicians were predominantly men (n = 160, 55.6%), with a median age of 38 years (interquartile range, 33-45 years), from Latin America (n = 112, 38.9%), Asia (n = 99, 34.4%), Africa (n = 52, 18.1%), or Eastern Europe (n = 25, 8.7%). The majority of responders were medical oncologists (n = 128, 44.4%), working mainly in academic hospitals (n = 135, 46.9%) and in the public sector (n = 170, 59.0%). Responders reported to have a median of 8 years of experience in medical practice (interquartile range, 4-15 years). A total of 47.6% (n = 137) were affiliated to a breast unit.

Knowledge, Practice, and Attitudes of Physicians Toward Fertility Preservation in Young Patients With Breast Cancer

Table 2 summarizes responses of study participants. A total of 59.7% of responders (n = 172) reported having sometimes consulted international guidelines on fertility preservation in patients with cancer and survivors (Fig 1). Regarding strategies for fertility preservation, 65.2% of responding physicians (n = 188) reported being knowledgeable or very knowledgeable on the use of luteinizing hormone-releasing hormone agonist (LHRHa) for ovarian function suppression during chemotherapy. Only 40.9% (n = 118), 32.3% (n = 93), and 28.1% (n = 81) considered to be well informed on oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation, respectively (Fig 2).

The possibility of impairing ovarian function and fertility with cytotoxic anticancer therapies was always or usually discussed with young patients with breast cancer by 71.6% of responding physicians (n = 207).

The primary reported factors preventing the access to the available fertility preservation procedures were the cost of the strategies (n = 185, 64.2%), the lack of collaboration with a specialized center for medically assisted reproduction (n = 157, 54.5%), patient-related factors (age, social status, instruction, availability of a partner, prior children, and cancer prognosis; n = 148, 51.4%), the lack of information about these procedures (n = 79, 27.4%), and being worried about delaying the start of chemotherapy (n = 69, 24.0%).

Among responding physicians, 43.8% (n = 126) reported that LHRHa was available and its cost covered or partially covered by the national health system or by their institution. However, oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation were covered for less than 10% of responders (7.6%, 4.2%, and 4.2%, respectively; Fig 3).

LHRHa administration, oocyte cryopreservation, embryo cryopreservation, and ovarian tissue cryopreservation were always or usually suggested to young women with breast cancer interested in preserving fertility by 80.2% (n = 231), 49.3% (n = 142), 28.8% (n = 83), and 27.8% (n = 80) of physicians, respectively (Fig 4).

Attitudes toward the safety of controlled ovarian stimulation (COS) for embryo and/or oocyte cryopreservation were explored. It was considered a safe procedure in all patients by 42.4% of responding physicians (n = 122), whereas 29.9% (n = 86) and 18.1% (n = 52) of responders considered it not safe in patients with hormone receptor–positive breast cancer and in those candidates to neoadjuvant chemotherapy, respectively (Fig 5). A total of 76.4% (n = 220) agreed that cryopreservation of ovarian tissue should be performed only in centers with adequate expertise.

Among responding physicians, 33.7% (n = 97) and 17.7% (n = 51) agreed that ovarian suppression with LHRHa during chemotherapy should be proposed only to patients who cannot access embryo/oocyte cryopreservation or only to patients with hormone receptor–negative breast cancer, respectively.

Knowledge, Attitudes, and Practice of Physicians Toward Pregnancy After Breast Cancer Diagnosis and Treatment

Table 3 summarizes responses of study participants. For 43.8% of responders (n = 126), patient's pregnancy desire rarely alters the proposed systemic (neo)adjuvant treatment choice.

Attitudes of responding physicians toward pregnancy in survivors of breast cancer (ie, women previously affected by breast cancer) were explored. A total of 21.2% (n = 61) responding physicians considered that pregnancy might increase the risk of recurrence, particularly if it occurs within 2 years from cancer diagnosis (n = 92, 31.9%), and in patients with hormone receptor–positive disease (n = 73, 25.3%; Fig 6).

A total of 73.6% (n = 212) of responding physicians disagreed that abortion should be considered as a therapeutic option. A temporary interruption of endocrine therapy to allow pregnancy in patients with hormone receptor–positive disease was considered safe by 31.6% of responding physicians (n = 91). A total of 192 (66.7%) responders thought that a pregnancy in breast cancer survivors should

TABLE 1. Characteristics of Responding Physicians to the Survey

Characteristic	Responding Physicians, No. (%)
Age, years	
< 40	160 (55.6)
40-50	84 (29.2)
> 50	44 (15.3)
Age, years, median (IQR)	38 (33-45)
Sex	
Male	160 (55.6)
Female	128 (44.4)
Region of practice	
Africa	52 (18.1)
Latin America	112 (38.9)
Asia	99 (34.4)
Eastern Europe	25 (8.7)
Income[a]	
LIC	17 (5.9)
LMIC	117 (40.6)
UMIC	154 (53.5)
Speciality	
Medical oncology (including residents)	128 (44.4)
Surgical oncology	62 (21.5)
Radiation oncology (including residents)	78 (27.1)
General surgery	3 (1.0)
Internal and general medicine	5 (1.7)
Gynecology	4 (1.4)
Radiology	5 (1.7)
Other	3 (1.0)
Practice environment/1	
Academic general hospital	135 (46.9)
Non-academic general hospital	77 (26.7)
Specialized cancer center	73 (25.3)
Outpatient service	2 (0.7)
Other	1 (0.3)
Practice environment/2	
Public	170 (59.0)
Private	106 (36.8)
Both	12 (4.2)
Years of clinical practice, median (IQR)	8 (4-15)
Working in a breast unit	
Yes	137 (47.6)
No	151 (52.4)
New young patients with breast cancer (≤ 40 years) per month	
< 10	171 (59.4)
10-50	109 (37.8)
> 50	8 (2.8)

Abbreviations: IQR, interquartile range; LIC, low-income country; LMIC, lower- and middle-income country; UMIC, upper- and middle-income country.

[a]On the basis of the World Bank Classification (Venezuela was considered a UMIC on the basis of the last available classification and the survey time).

be considered as high-risk and 181 (62.8%) that breastfeeding was safe. Moreover, 55.9% (n = 161), 49% (n = 141), 46.2% (n = 133), and 47.25% (n = 136) of responders agreed that assisted reproductive technologies, COS, egg donation, and transplantation of cryopreserved ovarian tissue harvested at the time of diagnosis could be safely performed in breast cancer survivors, respectively (Fig 7).

DISCUSSION

In this survey, we investigated knowledge, practice, and attitudes of physicians practicing in LMICs toward fertility preservation and issues related to pregnancy after treatment completion in young women with breast cancer. We observed a suboptimal performance in dealing with these issues, thus highlighting the need to overcome the existing difficulties and increase awareness and education on these important aspects of the care of young patients.

In women diagnosed with cancer during reproductive years, oncofertility counseling is now considered standard of care.[15-17] However, prior surveys targeting mostly physicians practicing in Western countries have identified knowledge gaps in this domain.[20,28-31] In the present survey, we provide a picture of these important aspects of young women's care focusing specifically on physicians from LMICs. Additional issues were observed.

In patients interested in fertility preservation (ie, to increase their chances of having a future pregnancy), oocyte and embryo cryopreservation are the first options to be discussed, leaving ovarian tissue cryopreservation as an alternative in women who do not have enough time before starting an anticancer treatment or have contraindications to undergo the 10-15 days of COS.[15-17] Ovarian suppression with LHRHa during chemotherapy is now recognized as an established approach to reduce chemotherapy-induced POI but not a standalone fertility preservation strategy.[15-17]

TABLE 2. Knowledge, Practice, and Attitudes of Physicians Toward Fertility Preservation in Young Patients With Breast Cancer[a]

Q10. Have you ever consulted some international guidelines on fertility preservation in patients with cancer and survivors?

No, but I know where to find these guidelines, if needed	75 (26)
No, I am not aware of available guidelines on this topic	41 (14.2)
Yes	172 (59.7)

Q11. How would you describe your knowledge of the available strategies for fertility preservation in patients with breast cancer?

	Not at All Knowledgeable	Aware of But Not Much Knowledgeable	Knowledgeable	Very Knowledgeable
Ovarian suppression with LHRHa during chemotherapy	29 (10.1)	71 (24.7)	92 (31.9)	96 (33.3)
Embryo cryopreservation	72 (25)	123 (42.7)	78 (27.1)	15 (5.2)
Oocyte cryopreservation	55 (19.1)	115 (39.9)	95 (32.9)	23 (8)
Ovarian tissue cryopreservation	70 (24.3)	137 (47.6)	68 (23.6)	13 (4.5)

Q12. How often do you discuss the possible treatment-related impairment of ovarian function and fertility in young patients with breast cancer before starting cytotoxic anticancer therapies, especially when gonadal toxicity is expected?

Never	Rarely	Usually	Always
5 (1.7)	76 (26.4)	103 (35.5)	104 (36.1)

Q13. In your clinical practice, which is the main factor preventing the access to the available fertility preservation procedures? Please select all that apply (more than one response can be selected)

The cost of the available strategies for fertility preservation	185 (64.2)
Lack of collaboration with a specialized center for medically assisted reproduction	157 (54.5)
Patient-related factors: age, social status, instruction, availability of a partner, prior children, and cancer prognosis	157 (51.4)
Lack of information about these techniques in the oncology setting	79 (27.4)
Resistance of the medical team to any procedure that might delay the start of chemotherapy	69 (24)
The service is not continuously available (eg, shortage of workforce or medicines)	68 (23.6)
Religious or cultural barrier related to fertility preservation procedures	39 (13.5)
The only center is in the capital city or far from the setting where you practice	38 (13.2)
There are local centers for fertility preservation, but the referral time is long	36 (12.5)
Resistance of the medical team to allow pregnancy after breast cancer	33 (11.5)
Resistance of the medical team to any type of hormonal stimulation	23 (8.0)
The service is not available at all in my country	3 (1.0)
Lack of my awareness and insight	1 (0.3)

Q14. Which of the following fertility preservation procedures are available in your region and/or setting

	I Do Not Know	Not Available	Yes, But the Patient Would Have to Pay for the Procedure Unaffordably Out of Pocket	Yes, Covered or Partially Covered by the National Health System (or the institution) and Is Affordable for Patients
Ovarian suppression with LHRHa during chemotherapy	16 (5.6)	20 (6.9)	126 (43.8)	126 (43.8)
Embryo cryopreservation	54 (18.8)	84 (29.2)	138 (47.9)	12 (4.2)
Oocyte cryopreservation	38 (13.2)	68 (23.6)	160 (55.6)	22 (7.6)
Ovarian tissue cryopreservation	62 (21.5)	90 (31.3)	124 (43.1)	12 (4.2)

Q15. In young patients with breast cancer interested in preserving fertility, would you suggest the use of one or more of these procedures?

	Never	Rarely	Usually	Always
Ovarian suppression with LHRHa during chemotherapy	25 (8.7)	32 (11.1)	130 (45.1)	101 (35.1)
Embryo cryopreservation	104 (36.1)	101 (35.1)	53 (18.4)	30 (10.4)
Oocyte cryopreservation	49 (17)	97 (33.7)	96 (33.3)	46 (16)
Ovarian tissue cryopreservation	106 (36.8)	102 (35.4)	61 (21.2)	19 (6.6)

Q16. What are your attitudes toward the following statements?

	Disagree	Neutral	Agree
COS for embryo/oocyte cryopreservation should be considered safe in all patients	39 (13.5)	127 (44.1)	122 (42.4)
COS should NOT be considered safe in patients with hormone receptor–positive breast cancer	91 (31.6)	111 (38.5)	86 (29.9)
COS should NOT be considered safe in patients who are candidates to neoadjuvant chemotherapy	111 (38.5)	125 (43.4)	52 (18.1)
Cryopreservation of ovarian tissue should be performed only in centers with the adequate expertise	15 (5.2)	53 (18.4)	220 (76.4)
Ovarian suppression with LHRHa during chemotherapy should be proposed only to patients who cannot access embryo/oocyte cryopreservation	94 (32.6)	97 (33.7)	97 (33.7)
Ovarian suppression with LHRHa during chemotherapy should be proposed only to patients with hormone receptor–negative breast cancer	149 (51.7)	88 (30.6)	51 (17.7)

Abbreviations: COS, controlled ovarian stimulation; LHRHa, luteinizing hormone-releasing hormone agonist.
[a]No. (%).

Therefore, LHRHa during chemotherapy can be proposed not only to women with pregnancy desire after cryopreservation strategies but also to those concerned about the side effects of early menopause.[32,33]

In our survey, despite being involved in breast cancer care, approximately 40% of responding physicians had never consulted the available guidelines on fertility preservation in patients with cancer. Although most responders reported being well informed on the use of LHRHa during chemotherapy, only between 28% and 41% considered themselves to be knowledgeable or very knowledgeable about the three cryopreservation options, a poorer performance compared with the BCY survey.[20] Similar numbers were observed when assessing how often these different strategies were offered, with more than 80% reporting to always or usually propose the use of LHRHa during chemotherapy and only between 28% and 49% supporting referral to cryopreservation options. Notably, although approximately 44% of responding physicians mentioned that LHRHa during chemotherapy is available and its cost is covered or partially covered by their national health system or institution, this percentage went down to < 10% for cryopreservation options. This means that the recommended fertility preservation procedures were reported to be not covered, so to be not affordable, or simply not available by a high number of responding physicians. This is the most important and alarming gap between the present results and prior findings from the BCY survey.[20] Despite many requests to implement universal coverage for oncofertility services,[16,34] two thirds of responders to our survey considered the cost of fertility preservation strategies as the most frequent barrier in addressing these issues. Moreover, more than half of the responding physicians considered the lack of collaboration with a specialized center for medically assisted reproduction as another important limitation. In this regard, considering that the proportion of young women with breast cancer motivated to have access to fertility units for cryopreservation options is relatively small (approximately 10%-15% of all newly diagnosed

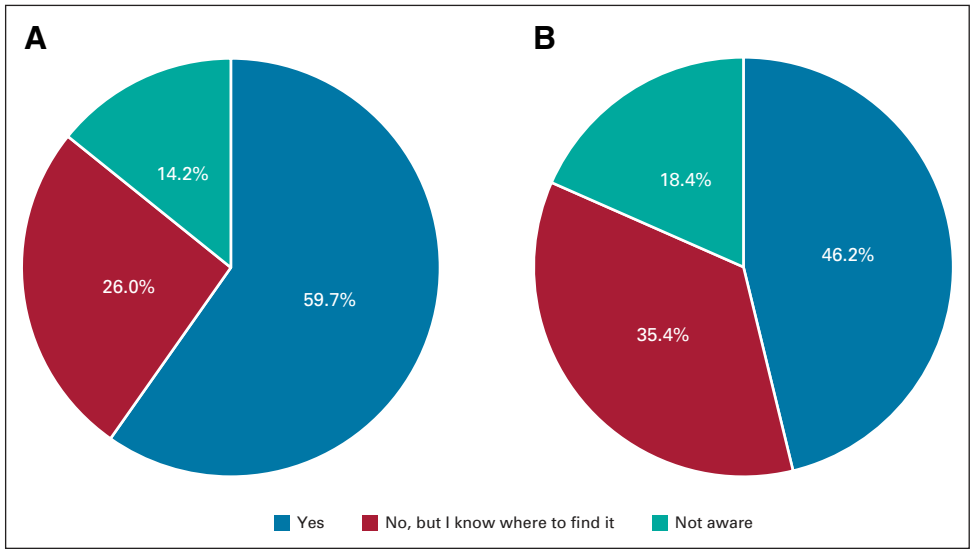


FIG 1. Physicians' knowledge on the available international guidelines on (A) fertility preservation and (B) pregnancy in breast cancer survivors.

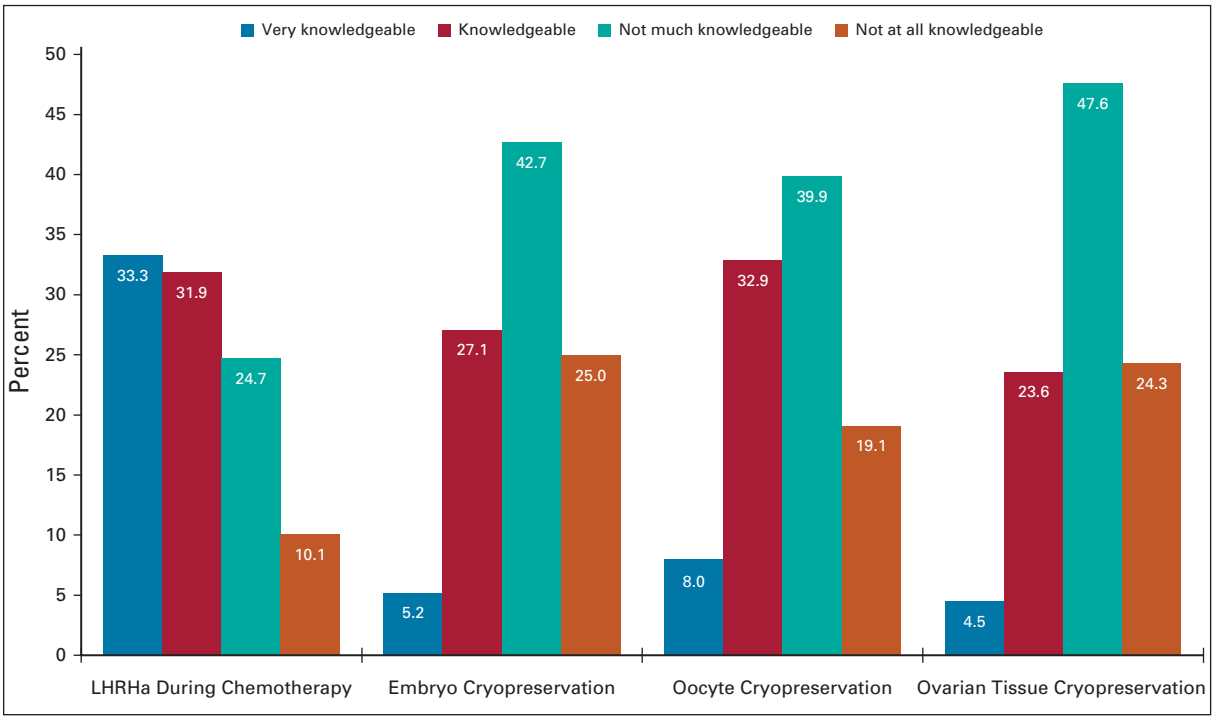


FIG 2. Physicians' knowledge on the available strategies for fertility preservation in patients with breast cancer. LHRHa, luteinizing hormone-releasing hormone agonist.

patients),[11-14] efforts are needed to overcome structural barriers, thus highlighting the importance of creating infrastructures to accommodate or link to multidisciplinary fertility units. A hub and spoke model with many oncology units referring patients interested in fertility preservation to few selected fertility centers might be preferable not only to

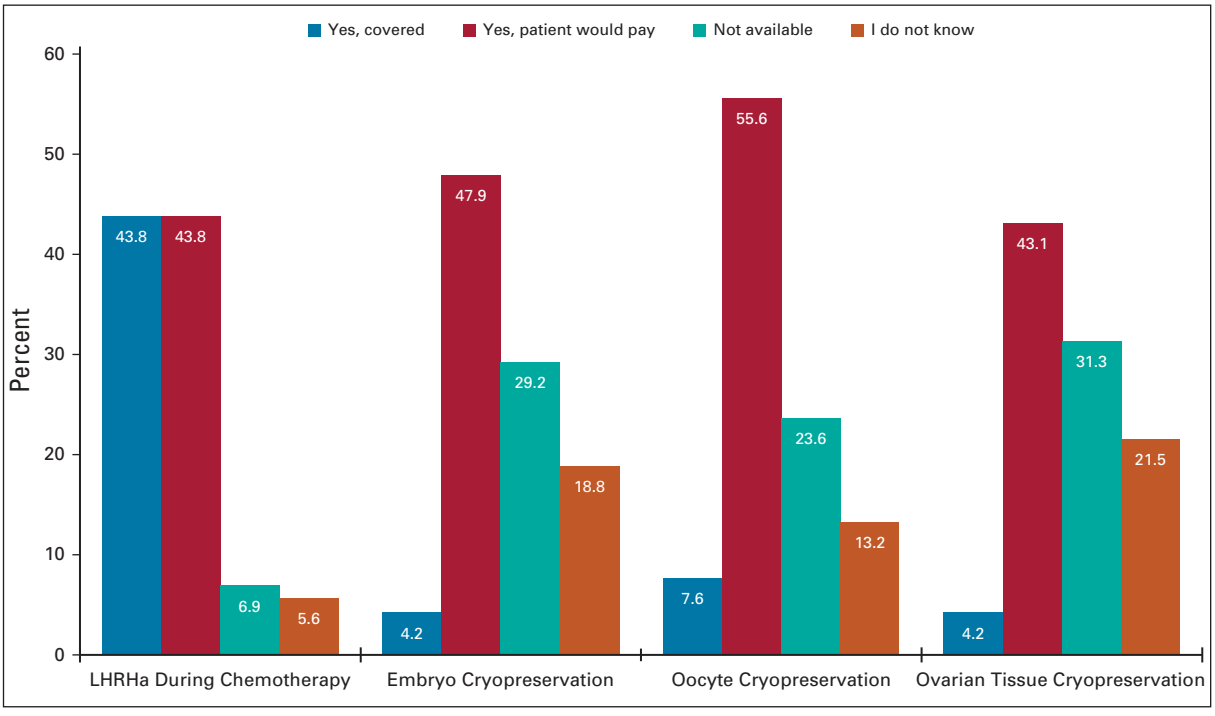


FIG 3. Availability and health care coverage of fertility preservation procedures among regions and/or settings. LHRHa, luteinizing hormone-releasing hormone agonist.

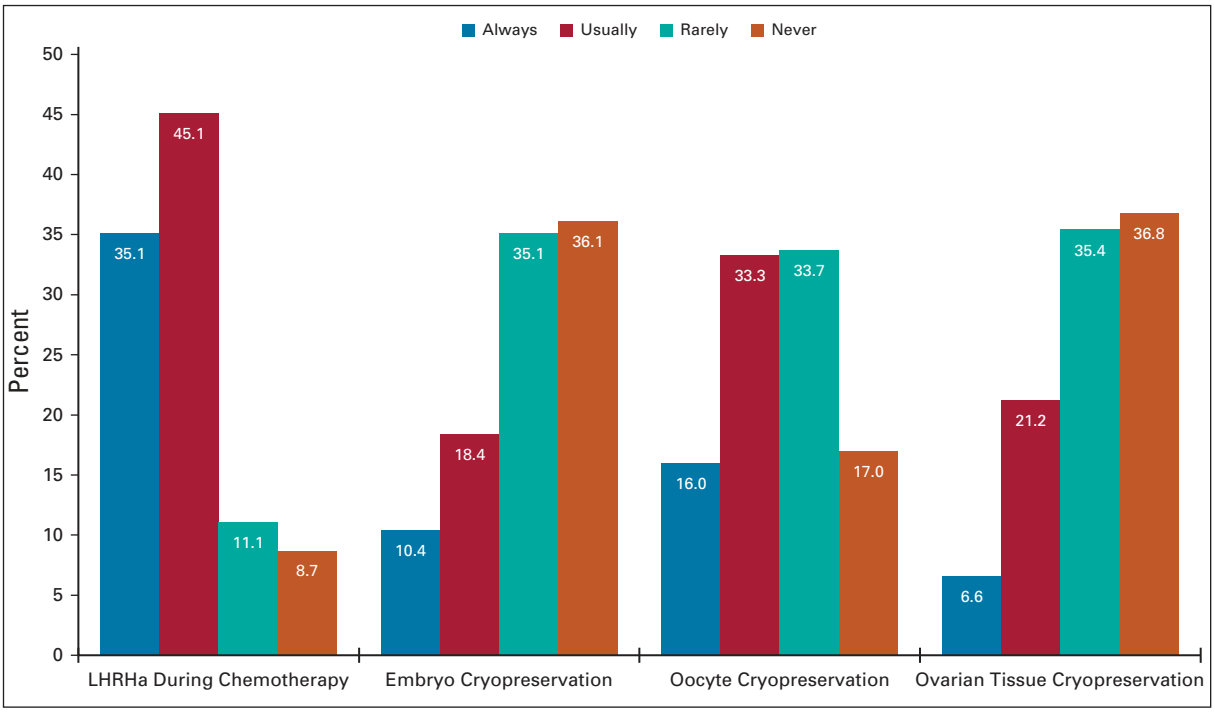
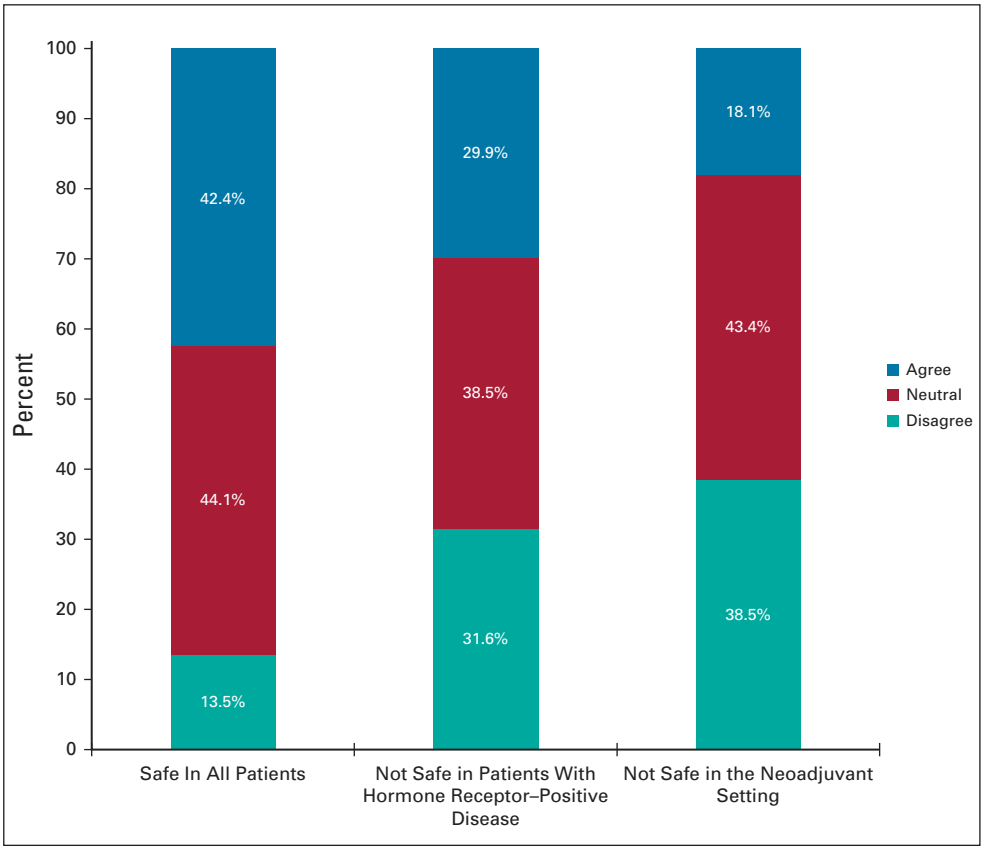


FIG 4. Frequency at which fertility preservation strategies are suggested by physicians in young women with breast cancer. LHRHa, luteinizing hormone-releasing hormone agonist.

FIG 5. Physicians' attitudes toward the safety of controlled ovarian stimulation in young women with breast cancer.



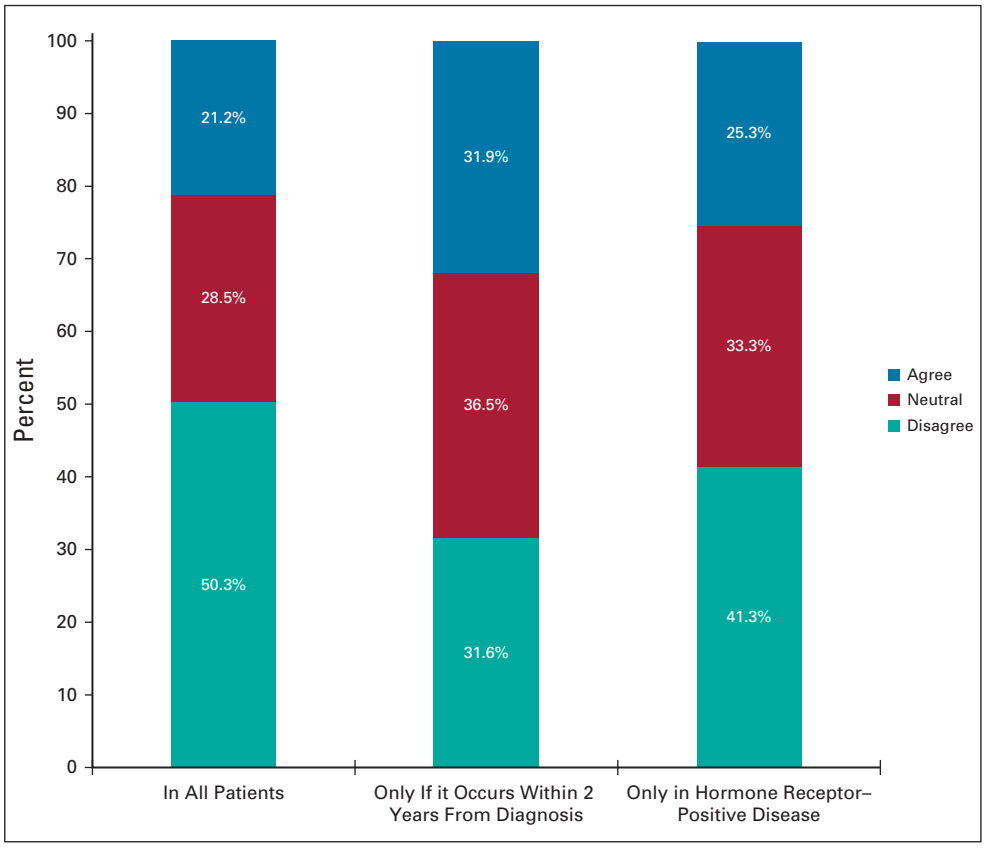


FIG 6. Physicians' attitudes toward the potential detrimental prognostic effect of pregnancy after breast cancer.

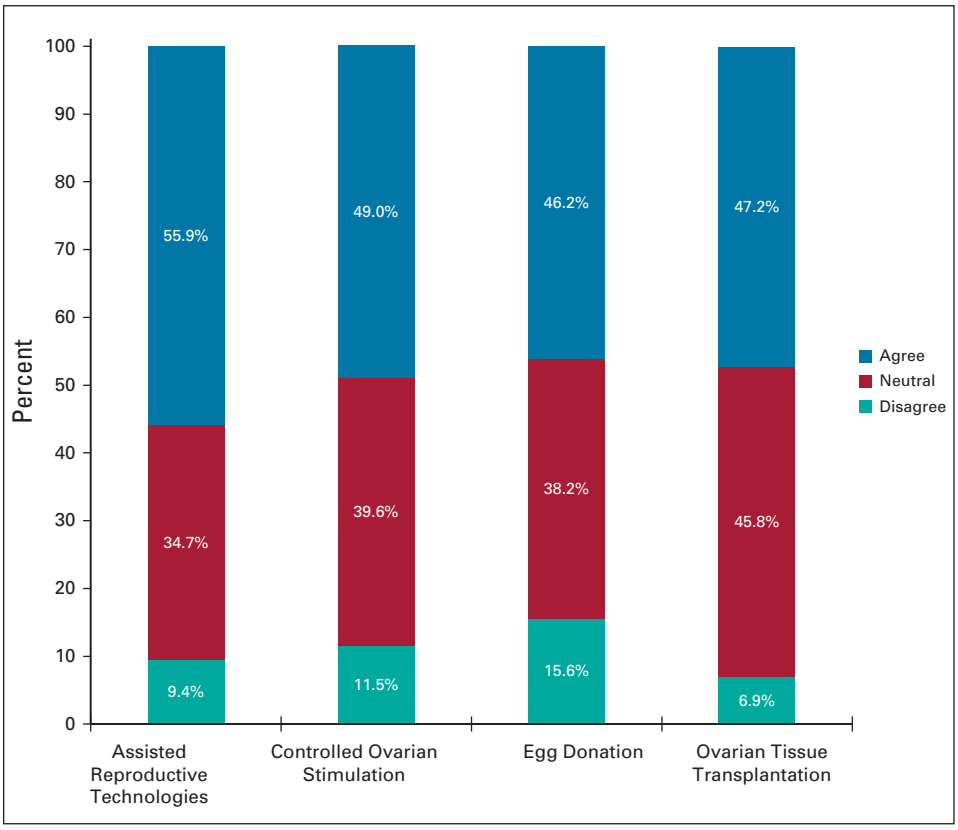


FIG 7. Physicians' attitudes toward the safety of different assisted reproductive strategies in breast cancer survivors.

TABLE 3. Knowledge, Attitudes, and Practice of Physicians Toward Pregnancy After Breast Cancer Diagnosis and Treatment[a]

Q17. Have you ever consulted the available international guidelines on the management of patients achieving a pregnancy after cancer diagnosis and treatment (ie, in cancer survivors)?

No, but I know where to find these guidelines, if needed	102 (35.4)
No, I am not aware of available guidelines on this topic	53 (18.4)
Yes	133 (46.2)

Q18. When you choose the systemic neoadjuvant/adjuvant treatment in women with breast cancer and wishing a pregnancy, would you alter the treatment to preserve fertility?

Never	Rarely	Usually	Always
66 (22.9)	126 (43.8)	82 (28.5)	14 (4.9)

Q19. What are your attitudes toward the following statements in women previously affected by breast cancer (ie, breast cancer survivors)?

	Disagree	Neutral	Agree
Abortion in breast cancer survivors is therapeutic and should be considered	212 (73.6)	59 (20.5)	17 (5.9)
A pregnancy in breast cancer survivors may increase the risk of recurrence	145 (50.3)	82 (28.5)	61 (21.2)
A pregnancy in breast cancer survivors may increase the risk of recurrence only if pregnancy occurs within 2 years from cancer diagnosis	91 (31.6)	105 (36.5)	92 (31.9)
A pregnancy in breast cancer survivors may increase the risk of recurrence only in patients with hormone receptor–positive disease	119 (41.3)	96 (33.3)	73 (25.3)
A temporary interruption of endocrine therapy to allow pregnancy in patients with hormone receptor–positive disease can be considered safe	77 (26.7)	120 (41.7)	91 (31.6)
A pregnancy in breast cancer survivors should be monitored and followed as high-risk pregnancy	43 (14.9)	53 (18.4)	192 (66.7)
Breastfeeding in breast cancer survivors is safe and can be promoted	27 (9.4)	80 (27.8)	181 (62.8)
Assisted reproductive technologies can be safely performed in breast cancer survivors	27 (9.4)	100 (34.7)	161 (55.9)
COS can be safely performed also in breast cancer survivors	33 (11.5)	114 (39.6)	141 (49)
Egg donation can be safely performed also in breast cancer survivors	45 (15.6)	110 (38.2)	133 (46.2)
Transplantation of cryopreserved ovarian tissue harvested at the time of diagnosis can be safely performed in breast cancer survivors to restore fertility	20 (6.9)	132 (45.8)	136 (47.2)

Abbreviation: COS, controlled ovarian stimulation.
[a]No. (%).

improve the chance of women to access these procedures but also in terms of cost optimization, to improve affordability, and should be envisioned worldwide including among LMICs.[35] Barriers were also determined by social determinants of health. More than half of the responders reported that social status and instruction might affect the likelihood of accessing oncofertility services. Reimbursement of oncofertility services should be pursued according to the available resources, along with patient-empowering educational interventions to enhance health literacy for shared decisions,[36] to enable patient-centered therapeutic plans and tackle cancer-related stigma, which is in part driven by the reduced pregnancy potential after anticancer treatments.[37]

Additionally, some misconceptions about the available strategies for ovarian function and/or fertility preservation were observed.

A high proportion of responding physicians (42.4%) was unsure that COS for embryo/oocyte cryopreservation is a safe procedure in patients with newly diagnosed breast cancer. Although data remain limited and deriving mainly from retrospective evidence, several studies have shown that one cycle of COS before starting chemotherapy is safe for young women with breast cancer.[38,39] This appears to be the case also for women with hormone receptor–positive breast cancer and/or those candidates to neoadjuvant chemotherapy.[38] In addition, to avoid potential concerns, the addition of letrozole to the protocols for COS has shown to significantly reduce estradiol levels while maintaining the efficacy of the procedure.[40] Therefore, the inclusion of letrozole in the protocols for COS is now supported as the preferred option in the breast cancer setting by all guidelines.[15-17]

Regarding the use of LHRHa during chemotherapy, it is important to highlight that this strategy has shown to be effective in reducing the risk of chemotherapy-induced POI while data on post-treatment pregnancies are more limited.[41] Therefore, it should be considered as an option for ovarian function preservation and not an alternative to cryopreservation strategies for women interested in fertility preservation.[10,33] Although some trials investigating this approach have excluded patients with hormone receptor–positive breast cancer,[32,42] the largest ones have included them.[43,44] Considering that giving LHRHa during chemotherapy is safe without worsening patients' outcomes and equally effective in patients with hormone receptor–positive and –negative disease,[45,46] it can be offered to all premenopausal patients with breast cancer interested in preserving ovarian function irrespective of the hormone receptor status of the tumor. Importantly, the use of LHRHa during chemotherapy in patients with hormone receptor–positive breast cancer, as also done in the TEXT trial,[46] may avoid the issues of assessing ovarian function at the time of chemotherapy completion to decide on the best adjuvant endocrine therapy approach.[47,48]

Many young women with breast cancer have not yet completed their family planning at the time of diagnosis and are interested in future motherhood.[49] However, breast cancer survivors have a lower likelihood of future

conception compared with the general population and patients diagnosed with other cancers.[50] In addition to the impact of breast cancer treatment on ovarian function, physicians' concerns on the safety of pregnancy after breast cancer should be considered important reasons for these findings.[20] This is confirmed in our survey in which only half of the responding physicians disagreed with the statement that pregnancy in these patients may increase the risk of recurrence, a percentage that lowered to 41% in the case of women with hormone receptor–positive breast cancer. These percentages were 69.6% and 63.0% in the BCY survey, suggesting more concerns in this regard among physicians practicing in LMICs.[20] These concerns are not supported by the growing amount of evidence that has become available showing that, after adequate treatment and period of follow-up, conceiving is safe for breast cancer survivors,[50,51] including among those with hormone receptor–positive disease.[52]

Approximately 32% of responding physicians agreed that a temporary interruption of endocrine therapy to allow pregnancy in patients with hormone receptor–positive disease could be considered safe. Notably, no solid evidence exists so far to counsel patients in this regard, and the results from the POSITIVE trial are awaited to shed light in this important area.[53,54]

Interestingly, approximately half of the responding physicians supported the safety of assisted reproductive technologies including COS for in vitro fertilization procedures in young breast cancer survivors. However, it should be highlighted that the safety data in this regard exist for newly diagnosed patients who are then candidates to undergo chemotherapy afterward,[38,39] whereas there is limited efficacy and safety evidence when these techniques are used following anticancer treatment completion.[55] Referring interested patients to fertility units before initiating anticancer therapies should remain the preferred approach.

Some limitations need to be considered when interpreting the results of our survey. It was not possible to estimate the correct response rate considering that different approaches were used in each country to try to reach as many colleagues as possible. We observed differences in response rates across the countries, and from some of them, only few physicians responded to the questionnaire. Moreover, most of responders were young and practiced primarily in academic hospitals and/or specialized cancer institutions. More than a third reported working in the private sector, probably mirroring a more optimistic scenario than in the real life. No information on knowledge, practice, and attitudes of nursing staff, patients, and their caregivers in these topics were collected.

However, we believe that our survey with its large sample size is unique in addressing these important aspects of the care of young women with breast cancer specifically among physicians practicing in LMICs. Information were obtained from a large number of countries, four different world regions, and completely different health care systems.

In conclusion, our survey provides an important picture of the current status on knowledge, practice, and attitudes of physicians practicing in LMICs toward fertility preservation and pregnancy after treatment completion in young women with breast cancer. Some important misconceptions were observed toward these issues. Targeted efforts in LMICs should be implemented to overcome barriers and to increase awareness and education for improving adherence to available guidelines and patients' oncofertility counseling.

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