

Prospective Study of Fertility Preservation in Young Women With Breast Cancer in Mexico

Cynthia Villarreal-Garza, MD, DSc^{1,2}; Fernanda Mesa-Chavez, MD^{1,2}; Alejandra Plata de la Mora, Psy, MSc^{2,3}; Melina Mijaya-Avila, Psy, PhD^{1,2}; Marisol Garcia-Garcia, MD^{1,2}; Alan Fonseca, MD^{2,3}; Sylvia de la Rosa-Pacheco, MD, MSc⁴; Marlid Cruz-Ramos, MD, PhD^{2,3}; Manuel Rolando García Garza, MD⁵; Alejandro Mohar, MD, DSc^{2,6,7}; and Enrique Bargallo-Rocha, MD^{2,3}

ABSTRACT

Background: Despite the risk of treatment-related infertility, implementation of fertility-preservation (FP) strategies among young patients with breast cancer is often suboptimal in resource-constrained settings such as Mexico. The “Joven & Fuerte: Program for Young Women With Breast Cancer” strives to enhance patient access to supportive care services, including FP measures through alliances with assisted-reproduction units and procurement of coverage of some of these strategies. This study describes patients from Joven & Fuerte who have preserved fertility, and assesses which characteristics were associated with the likelihood of undergoing FP. **Methods:** Women aged ≤40 years with recently diagnosed breast cancer were prospectively accrued. Sociodemographic and clinicopathologic data were collected from patient-reported and provider-recorded information at diagnosis and 1-year follow-up. Descriptive statistics, chi-square test, and simple logistic regression were used to compare patients who preserved fertility with those who did not. **Results:** In total, 447 patients were included, among which 53 (12%) preserved fertility, representing 38% of the 140 women who desired future biologic children. Oocyte/embryo cryopreservation was the most frequently used method for FP (59%), followed by temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy (26%), and use of both GnRHa and oocyte/embryo cryopreservation (15%). Younger age, higher educational level, being employed, having private healthcare insurance, and having one or no children were associated with a significantly higher likelihood of preserving fertility. **Conclusions:** By facilitating referral and seeking funds and special discounts for underserved patients, supportive care programs for young women with breast cancer can play a crucial role on enhancing access to oncofertility services that would otherwise be prohibitive because of their high costs, particularly in resource-constrained settings. For these efforts to be successful and widely applied in the long term, sustained and extended governmental coverage of FP options for this young group is warranted.

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Background

Breast cancer is the most commonly diagnosed malignancy among women of childbearing age.¹ In developed countries, approximately 7% of breast cancer cases are diagnosed in young women,² whereas in less thriving settings such as Mexico this rate reaches up to 15%.³

Among the unique age-related challenges that young women with breast cancer (YWBC) face, almost half report unmet parity at diagnosis, a rate that has been reproduced in Mexican patients.^{4,5} Therefore, potential treatment-related premature ovarian failure and fertility loss are particularly relevant and can cause significant psychologic distress in this group.^{6,7}

For this reason, national and international guidelines recommend that physicians discuss the treatment-related risk of infertility with patients of reproductive age to aid them with fertility preservation (FP) decisions as early as possible.^{8–10} Additionally, clinicians must refer those interested in having children to preservation specialists promptly^{8,9} so they can undertake strategies such as cryopreservation and temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy.¹¹ However, adherence to these recommendations is often suboptimal in limited-resource countries such as Mexico, presumably because of physicians' lack of knowledge regarding the safety of preservation methods and pregnancy after BC, financial hindrances, scarcity of specialists, and lack of partnerships with reproductive units.^{12–14}

Moreover, in resource-constrained settings such as Mexico, cancer control efforts are mainly focused on providing medical treatment, generally bypassing the survivorship aspects of care.¹⁵ Additionally, preservation strategies are seldom covered by private or governmental healthcare insurances and are unaffordable for most underserved populations.^{4,16}

To address these barriers, the “Joven & Fuerte (Mexican Young & Strong): Program for Young Women With Breast Cancer” (J&F) was created in 2014 as the first specialized Latin American program with the goal of comprehensively characterizing a prospective cohort of YWBC, assessing their needs, and offering them supportive care

¹Centro de Cancer de Mama, TecSalud, Tecnológico de Monterrey, San Pedro Garza García, Nuevo Leon; ²Joven & Fuerte, Programa para la Atención e Investigación para Pacientes Jóvenes con Cáncer de Mama en México, Ciudad de México; ³Departamento de Tumores Mamarios e Investigación, Instituto Nacional de Cancerología, Ciudad de México; ⁴Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Nuevo Leon; ⁵Instituto de Ginecología, TecSalud, Tecnológico de Monterrey, Monterrey, Nuevo Leon; and ⁶Unidad de Epidemiología e Investigación Biomédica en Cáncer, Instituto Nacional de Cancerología, and ⁷Instituto de Biomedicas, Universidad Nacional Autónoma de México, Ciudad de México, México.

services, including enhanced access to FP.¹⁵ This study describes patients from J&F who have undergone FP and assesses which sociodemographic and clinicopathologic features were associated with the likelihood of preserving fertility.

Methods

Description of J&F

J&F is currently active at 3 sites: Instituto Nacional de Cancerología (INCan) in Mexico City and Hospital San José (HSJ) and Hospital Zambrano Hellion (HZH) in Monterrey. The program also receives patients interested in FP referred from Fundación de Cáncer de Mama and Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran in Mexico City. The Mexico City sites and HSJ provide care for patients with public healthcare insurance, whereas HZH receives those with private coverage.

Women aged ≤ 40 years with recently diagnosed breast cancer are invited to participate in J&F. The navigator discusses and provides educational material regarding relevant issues for YWBC, identifies patients' needs, and assists in making early referrals to oncofertility, genetic counseling, and psycho-oncology, as needed. Additionally, patients are invited to participate in the prospective cohort for research purposes. A detailed description of the structure and functioning of J&F has been published previously.¹⁵

Specifically, to deliver oncofertility services, J&F has established local alliances with assisted-reproduction units, which provide special-price cryopreservation procedures for underserved patients enrolled in the program. Additionally, for some patients, the coverage of preservation strategies has been possible through governmental support. In this way, J&F has enhanced access to specialized FP methods that would otherwise be prohibitive due to their high costs. Regarding GnRHa, their use for FP purposes is not covered in some institutions, and they represent an out-of-pocket expense for patients.

Study Design

This study was developed based on the J&F prospective cohort. All participants enrolled up to June 2019 were eligible. Data for this analysis were collected from patient-reported information at diagnosis/baseline (age, educational level, employment status, partnership status, number of children, medical affiliation, desire of future biologic children), and provider-recorded data at baseline (clinical stage, breast cancer subtype) and 1-year follow-up (patient use of FP methods, oncologic treatment).

Statistical Analysis

Patients were categorized into 2 groups: use versus nonuse of a preservation strategy (oocyte/embryo cryopreservation

and/or GnRHa for FP). Descriptive statistics were used to analyze the sociodemographic and clinicopathologic characteristics of each group. These variables were then compared between groups using a chi-square test. Simple logistic regression using complete-case analysis was conducted and odds ratios (ORs) and 95% confidence intervals were calculated to determine the likelihood of preserving fertility. The same analysis was performed to compare patients who underwent FP with those who desired future biologic children at diagnosis but did not preserve fertility. A P value $<.05$ was significant. Statistical analysis was performed using SPSS Statistics, version 25 (IBM Corp).

Additionally, the following time intervals were calculated: diagnosis to neoadjuvant chemotherapy initiation, diagnosis to surgery, and surgery to adjuvant systemic therapy initiation. Medians were compared between patients who underwent cryopreservation and those who did not to determine whether any delays occurred in the start of oncologic treatment as a result of FP.

Results

This study included 447 patients, 265 (59%) from the Mexico City sites (mainly from INCan), 140 (31%) from HSJ, and 42 (9%) from HZH. Median age at diagnosis was 36 years. Most participants had at least a high school education (57%), were unemployed/housewives (65%), were publicly insured (90%), and were married/in domestic partnerships (64%). At diagnosis, 21% were childless and 31% desired (more) biologic children. Table 1 shows participants' remaining characteristics.

Of the total patients, 53 (12%) underwent FP, representing 38% of the 140 who desired future biologic children at the time of the baseline survey. Of these 53 patients, 28 (53%) were enrolled at the Mexico City sites, 12 (23%) at HSJ, and 13 (25%) at HZH. Oocyte/embryo cryopreservation was the most frequently used method (59%), followed by temporary ovarian suppression with GnRHa during chemotherapy (26%), and oocyte/embryo cryopreservation along with GnRHa (15%; Figure 1).

At the Mexico City sites, 25 (89%) patients underwent oocyte/embryo cryopreservation (22 provided through a dedicated governmental fund, at no cost to patients) and 6 (21%) received GnRHa (all covered by the public healthcare system). At HSJ, 7 (58%) cryopreserved oocytes/embryos (5 offered with a special discount) and 6 (50%) used GnRHa (all covered out-of-pocket by patients). At HZH, 7 (54%) underwent cryopreservation (all paid for by patients) and 10 (77%) used GnRHa (covered by private insurances).

Patient characteristics associated with a significantly higher likelihood of preserving fertility were age ≤ 36 years (OR, 3.0; 95% CI, 1.5–6.1), having at least high school education (OR, 15.7; 95% CI, 4.7–65.6), being

Table 1. Sociodemographic and Clinical Characteristics of Patient Cohort

Characteristic	n (%)
Total, n	447
Age, median (range), y	36 (32–38)
Educational level	
No schooling	2 (0.4)
Elementary school	40 (8.9)
Middle school	107 (23.9)
High school	69 (15.4)
Technical career	39 (8.7)
Undergraduate or college	128 (28.6)
Postgraduate	20 (4.5)
Missing	42 (9.4)
Employment status	
Employed	140 (31.3)
Unemployed/Housewife	292 (65.3)
Student	15 (3.4)
Disabled	19 (4.3)
Missing	11 (2.5)
Insurance status	
Public insurance	402 (89.9)
Private insurance	42 (9.4)
Missing	3 (0.7)
Partnership status	
Unpartnered	132 (29.5)
Partnered	287 (64.2)
Missing	28 (6.3)
Number of children	
None	92 (20.6)
1	87 (19.5)
≥2	240 (53.7)
Missing	28 (6.3)

(continued)

employed (OR, 3.9; 95% CI, 2.1–7.2), having private insurance (OR, 4.3; 95% CI, 2.0–9.1), and having one or no children (OR, 26.8; 95% CI, 6.0–119.4, and OR, 63.5; 95% CI, 14.8–272.3, respectively). When considering only patients who desired future biologic children, the same variables were significantly associated with a higher likelihood of pursuing FP, except for age ≤36 years (Table 2).

Of the 87 patients who wanted (more) biologic children but did not preserve fertility, 38 (44%) reported the following reasons for not doing so: needing to start cancer treatment immediately ($n=19$; 22%), personal reasons ($n=11$; 13%), and financial issues ($n=10$; 11%). Among patients from Mexico City, financial issues

Table 1. Sociodemographic and Clinical Characteristics of Patient Cohort (cont.)

Characteristic	n (%)
Desire to have (more) biologic children at diagnosis	
Yes	140 (31.3)
No	307 (68.7)
Clinical stage	
0	5 (1.1)
I	54 (12.1)
II	199 (44.5)
III	151 (33.8)
IV	34 (7.6)
Missing	4 (0.9)
Breast cancer subtype	
HR+/HER2-	234 (52.3)
HR+/HER2+	69 (15.4)
HR-/HER2+	28 (6.3)
Triple-negative	110 (24.6)
Missing	7 (1.6)
Treatment	
Chemotherapy	363 (81.2)
Radiotherapy	268 (59.9)
Endocrine therapy	238 (53.2)
Anti-HER2 therapy	84 (18.8)

Abbreviation: HR, hormone receptor.

were the main reason for 13%, whereas among those from Monterrey, where all preservation strategies were covered by patients, finances represented the main barrier for 47%.

Regarding the systemic treatment prescribed to patients who underwent FP, 83% received chemotherapy and 55% endocrine therapy. No significant difference in treatments received was found between patients who preserved fertility and those who did not.

In total, 39 of 53 (74%) patients used cryopreservation as their FP method: 10 (26%) before receiving neoadjuvant chemotherapy, 10 (26%) before surgery and adjuvant treatment, and 19 (49%) after surgery but before adjuvant treatment. Accordingly, the following median intervals were observed: diagnosis to neoadjuvant chemotherapy, 39 days (range, 25–68 days); diagnosis to surgery, 44.5 days (range, 18–80 days); and surgery to adjuvant systemic therapy, 46 days (range, 16–85 days). The corresponding median intervals for patients who did not preserve fertility or who only used GnRHa for FP were 32.5 days (range, 3–89 days), 42 days (range, 3–162 days), and 41 days (range, 4–129 days), respectively.

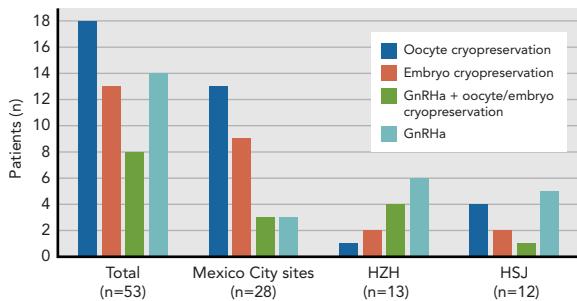


Figure 1. Strategies for fertility preservation in young women with breast cancer from “Joven & Fuerte.”

Abbreviations: GnRHa, gonadotropin-releasing hormone agonists; HSJ, Hospital San Jose; HZH, Hospital Zambrano Hellion.

Discussion

Although an integral component of cancer care, the implementation of oncofertility practices among YWBC in resource-constrained settings has not become as widespread as in higher income countries.^{17,18} However, this study suggests that specialized supportive care programs that enhance access to preservation procedures for these patients may play a crucial role in reducing that gap.

During a 4-year period, 12% of the J&F patients underwent FP. This proportion is similar to that described in the HOHO cohort, in which FP measures, including GnRHa use, were practiced among 10% of patients.¹⁹ Moreover, this rate represents a significant increase in FP compared with the <1% previously reported by our group when J&F was not yet underway.⁴ Importantly, in a recent cross-sectional study exploring patients’ perspectives of J&F, most participants (81%) recalled being informed about the treatment-associated fertility risks.²⁰ In contrast, prior to the initiation of J&F only 31% of YWBC reported having received this information.⁴ These differences display the positive impact a dedicated program for YWBC can have on promoting a higher number of discussions about reproductive issues and, consequently, more FP referrals, as has also been demonstrated by previous studies in developed countries.^{21,22}

More specifically, and possibly of more relevance than the overall implementation rate of FP in this cohort, 38% of those patients who desired future children were assisted to receive a preservation strategy, a percentage similar to the 31% reported by a German study of cancer patients in general.²³ Furthermore, in 70% of the J&F cases, the strategy involved oocyte/embryo cryopreservation, the first-line options for FP in patients with cancer.^{8,11,24} This proportion may be explained by the coverage of cryopreservation procedures through a dedicated governmental fund at one of the J&F sites, as well as the alliances that the program fosters with 4 assisted-reproduction centers in Mexico that facilitate referral and provide special discounts for underserved patients who cannot cover these measures’ total costs.

It should also be noted that only 41% of the patients who preserved fertility received GnRHa. This percentage contrasts with current practices in other countries such as Italy, where all YWBC are granted coverage for temporary ovarian suppression with GnRHa during chemotherapy and their use reaches rates of 98%.^{25,26} GnRHa are a less expensive, effective, and safe second-line measure for women who have no access, refuse, or have contraindications to cryopreservation procedures.^{16,27–29} Implementing their routine use in the Mexican context, however, is challenging, possibly due to 2 main reasons. First, not all Mexican physicians discuss reproductive issues with YWBC, and a substantial proportion wrongly believe that GnRHa are detrimental to their prognosis.¹⁴ Second, GnRHa are seldom covered by public insurances and most patients either lack the resources to afford them or are forced to choose between cryopreserving or receiving GnRHa because of financial constraints. Support from the Mexican public healthcare system through coverage of GnRHa for FP purposes among YWBC, following the examples of countries such as Italy, Sweden, and Israel,^{25,30,31} would aid considerably in addressing this need.

In 2 previous studies from developed countries, the most influential factors in patients’ decision to preserve fertility were insurance coverage of the procedures, the ability to pay for them,¹⁹ and believing prompt cancer treatment initiation was a priority.³² Similarly, our patients’ main reasons for not undergoing FP even when they desired future biologic children were the perception of needing to start cancer treatment rapidly, personal reasons, and financial issues.

Notably, 27% of the patients who underwent cryopreservation received neoadjuvant chemotherapy, suggesting that the possibility of delaying this treatment was not a definitive reason to reject FP for a considerable proportion of patients. In this regard, it should be highlighted that no considerable differences were found between patients who cryopreserved and those who did not in terms of the intervals from diagnosis to neoadjuvant chemotherapy initiation (39 vs 32.5 days), from diagnosis to surgery (44.5 vs 42 days), or from surgery to adjuvant treatment initiation (46 vs 41 days). According to these findings, undergoing cryopreservation probably does not entail a risk of delaying oncologic treatment. Therefore, it should not represent a decisive factor during patients’ and physicians’ decision-making when considering FP.

Moreover, the median interval between diagnosis and the start of oncologic treatment was similar to that reported in another study concerning oncofertility and delays in neoadjuvant chemotherapy initiation.³³ Data are limited regarding the security and outcomes of postponing neoadjuvant chemotherapy to perform FP in patients with breast cancer.³³ Even though some studies state that this practice is probably safe,^{30,34,35} most patients and

Table 2. Association Between Patient Characteristics and Use of an FP Strategy

Characteristic	FP n (%)	Complete Cohort			Patients Who Desired Future Biologic Children at Diagnosis		
		No FP n (%)	OR (95% CI)	Chi-Square P Value	No FP n (%)	OR (95% CI)	Chi-Square P Value
Total, n	53	394			87		
Age at diagnosis				.001			.255
>36 y	13 (25)	172 (46)	Ref		27 (31)	Ref	
≤36 y	39 (75)	200 (54)	3.0 (1.5–6.1)		60 (69)	1.59 (0.71–3.58)	
Educational level				<.001			<.001
Middle school or less	2 (4)	147 (41)	Ref		27 (31)	Ref	
High school or greater	45 (96)	211 (59)	15.7 (4.7–65.6)		59 (69)	10.3 (2.32–45.5)	
Employment status							
Employed	31 (62)	109 (30)	3.9 (2.1–7.2) ^a	<.001	28 (32)	3.43 (1.66–7.11) ^a	.001
Unemployed/Housewife	21 (42)	271 (73)	0.3 (0.1–0.5) ^a	<.001	57 (66)	2.62 (1.28–5.36) ^a	.007
Student	2 (4)	13 (4)	1.1 (0.3–5.2) ^a	.865	7 (8)	2.1 (0.41–10.52) ^a	.357
Disabled	2 (4)	17 (5)	0.9 (0.2–3.9) ^a	.846	5 (6)	1.46 (0.27–7.83) ^a	.655
Insurance status				<.001			.002
Public insurance	37 (76)	355 (93)	Ref		81 (94)	Ref	
Private insurance	12 (24)	27 (7)	4.3 (2.0–9.1)		5 (6)	5.25 (1.72–15.9)	
Partnership status				.089			.562
Unpartnered	21 (42)	111 (30)	Ref		41 (47)	Ref	
Partnered	29 (58)	258 (70)	0.6 (0.3–1.1)		46 (53)	1.23 (0.61–2.48)	
Number of children				<.001			.001
≥2	2 (4)	238 (65)	Ref		25 (29)	Ref	
1	16 (32)	71 (19)	26.8 (6.0–119.4)		27 (31)	11.42 (2.5–52.1)	
None	32 (64)	60 (16)	63.5 (14.8–272.3)		35 (40)	7.4 (1.54–35.51)	
Clinical stage				.038			.109
0	1 (2)	4 (1)	Ref		1 (1)	Ref	
I	11 (22)	43 (11)	1.0 (0.1–10.1)		10 (12)	1.1 (0.06–20)	
II	27 (53)	172 (44)	0.6 (0.6–5.4)		35 (40)	0.71 (0.04–11.9)	
III	11 (22)	140 (36)	0.3 (0.03–3.1)		38 (44)	0.28 (0.01–5)	
IV	1 (2)	33 (8)	0.1 (0.006–2.3)		3 (3)	0.3 (0.009–11.9)	
Breast cancer subtype				.513			.912
HR+/HER2-	27 (54)	207 (53)	Ref		47 (55)	Ref	
HR+/HER+	11 (22)	58 (15)	1.3 (0.6–2.9)		15 (17)	1.16 (0.45–2.94)	
HR-/HER2+	2 (4)	26 (7)	0.6 (0.1–2.6)		5 (6)	0.69 (0.12–3.83)	
Triple-negative	10 (20)	100 (25)	0.7 (0.3–1.5)		19 (22)	0.82 (0.32–2.07)	

Abbreviations: FP, fertility preservation; HR, hormone receptor; OR, odds ratio.

^aParticipants could select more than one answer for this question. Therefore, reference values correspond to those who were not employed, not unemployed, not students, and not disabled, respectively.

providers are reluctant to delay chemotherapy.³⁶ This is particularly relevant in developing countries, in which YWBC frequently present with locally advanced breast cancer that requires neoadjuvant chemotherapy,^{37,38} which might influence decision-making processes regarding FP. Notably, in a context unrelated to FP, 2 studies reported that a delay in neoadjuvant chemotherapy initiation of

≥56 or ≥61 days was associated with an increased risk of death.^{39,40} Considering this, our patients are probably in a safe time frame given that their median time to neoadjuvant chemotherapy was 39 days, with only 1 patient presenting an interval of ≥56 days.

Of note, in relation to financial concerns, more than half of these patients' preservation methods were provided

at no cost or with special discounts. Additionally, in Monterrey, where patients had to pay for all strategies, a higher proportion listed financial reasons as their main impediment to undergoing FP. Therefore, the extent to which finances represent a barrier for Mexican patients is probably greater than what is reported by this cohort.

According to our comparative analysis, younger age, higher educational level, and being employed were each associated with a higher likelihood of undergoing FP. These characteristics have been previously associated with more fertility concerns and may play a role in the decision-making of YWBC who are interested in preserving fertility.⁷ Moreover, these features could be interrelated, as better-educated women tend to pursue career development and delay childbearing.^{41–43} Hence, YWBC with these characteristics might not have children yet and may be more interested in pursuing FP.

Regarding parity, patients who had one or, especially, no children, were the most likely to preserve fertility. Other studies have also reported that nulliparous YWBC were more likely to have fertility concerns, to desire future children, and to consider seeking FP.^{7,44} In contrast, others have documented that parity did not affect fertility referrals and was not a predictive factor for undergoing FP.^{45,46} Still, considering that being childless at diagnosis was the most prominent predictor of pursuing FP in the present study, physicians could give special emphasis to the treatment-related risk of infertility and the available preservation options among nulliparous patients.

Another finding from this study, although not statistically significant, was a trend toward lower odds of preserving fertility as patients' clinical stage increased. This pattern was also observed in another multicenter analysis that found that patients with lower-stage breast cancer pursued FP more often.⁴⁷ A possible explanation may be that physicians favor discussing fertility issues and making oncofertility referrals when patients have early-stage breast cancer.⁴⁵ Remarkably, despite this trend, one J&F patient with metastases underwent cryopreservation, which highlights the importance of addressing patients' reproductive concerns on a case-by-case basis and offering FP methods to all young patients, irrespectively of their disease stage.⁴⁸ Nonetheless, FP in patients with poor prognosis raises significant ethical dilemmas, such as the morality of denying FP when life expectancy is limited, the possibility of instilling false hopes of survival by offering FP options, and the matter of coverage for these strategies.⁴⁹ Importantly, given that a reduced lifespan is usually not a sufficient reason to withhold reproductive assistance,^{50,51} physicians' main role should be to help patients make an informed, conscious choice by ensuring their appropriate understanding of prognosis, values and priorities, cost of procedures, and future arrangements for the child's welfare, always respecting patient autonomy.^{52–54}

As previously emphasized by others, fertility concerns are not limited to patients who possess specific characteristics.^{4,55} Patients' features must not be regarded as determinants when physicians consider addressing reproductive issues and making referrals to oncofertility units. On the contrary, all YWBC must be informed about these topics and offered FP options, regardless of physicians' preconceptions.

This study has important strengths and limitations. The main positive aspects include its prospective and longitudinal design and the recruitment of patients from 3 of the country's main breast cancer referral centers. Additionally, it provides evidence that asserts the benefits and need for dedicated programs for YWBC. However, given that the studied population belongs to a special supportive care program for this young group, their results could differ substantially from patients who are not members of similar organizations. Last, other unmeasured variables possibly exist between patients who preserved fertility and those who did not, including rates of referral to oncofertility counseling, time between referral and appointments, and the impact of such consultations on FP decision-making, which could influence patients' likelihood of undergoing FP.

Conclusions

This study represents the largest FP report from a prospective cohort of YWBC in a resource-constrained country. Among these patients, younger age, higher educational level, being employed, being privately insured, and having 1 or no children were associated with a higher likelihood of preserving fertility. These characteristics should not be regarded as determinant identifiers of patients who will pursue FP, but they may aid oncologists in recognizing women with whom fertility issues and preservation strategies should be particularly underscored.

Furthermore, these findings suggest that median intervals until oncologic treatment initiation do not differ between women who cryopreserve and those who do not. With this information, physicians might reassure patients that the time needed for FP should not delay the start of their oncologic treatment or negatively impact their outcomes. Hence, this concern should not be a decisive factor for patients or clinicians when considering FP. Nonetheless, this observation should be explored in future studies and efforts should be made to decrease these intervals further.

Finally, this study also highlights the transcendence that a directed, supportive care program for YWBC can have on enhancing access to specialized oncofertility services, particularly in limited-resource settings. Certainly, increased physician awareness and advocacy for FP in YWBC are needed for these efforts to be successful and widely applied in the long term. Moreover, sustained and extended governmental support, like that offered in other countries, is warranted for the routine coverage of

FP for YWBC. These practices will ultimately translate into delivering integral care to this group.

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