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# Original article

# Fertility concerns among breast cancer patients in Mexico



Cynthia Villarreal-Garza <sup>a, b, c</sup>, Bertha Alejandra Martinez-Cannon <sup>b, c</sup>, Alejandra Platas <sup>c</sup>, Alejandro Mohar <sup>a, c</sup>, Ann H. Partridge <sup>d</sup>, Arnoldo Gil-Moran <sup>b</sup>, Alan Fonseca <sup>c</sup>, Yoatzin Vega <sup>c</sup>, Enrique Bargallo-Rocha <sup>a, c</sup>, Servando Cardona-Huerta <sup>b</sup>, Yadira Estefany Lopez-Aguirre <sup>a, c</sup>, Regina Barragan-Carrillo <sup>b, c</sup>, Andrea Castro-Sanchez <sup>c, e, \*</sup>

- a Departamento de Investigacion y de Tumores Mamarios, Instituto Nacional de Cancerologia, Mexico City, Mexico
- <sup>b</sup> Centro de Cancer de Mama, Tecnologico de Monterrey, Monterrey, N.L., Mexico
- <sup>c</sup> Joven y Fuerte: Programa para la Atencion e Investigacion de Mujeres Jovenes con Cancer de Mama, Mexico City, Mexico
- <sup>d</sup> Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
- e Catedras CONACYT, Instituto Nacional de Cancerologia, Mexico

## ARTICLE INFO

Article history: Received 26 January 2017 Received in revised form 18 February 2017 Accepted 20 February 2017

Keywords: Breast neoplasm Fertility preservation Quality of life Young women Mexico

#### ABSTRACT

*Objective:* Young women represent a high proportion of the total number of breast cancer (BC) patients in Mexico; however, no previous studies addressing their attitudes regarding the risk of chemotherapy-induced infertility and its contributing factors are available. The aim of this study was to evaluate the concerns of young women with BC towards the risk of infertility in two referral centers in Mexico with access to public health services.

*Methods*: A cross-sectional study including women with newly or previously detected BC aged 40 years or younger at diagnosis was conducted. Variables regarding concerns about fertility were collected from an adapted version of the Fertility Issues Survey.

*Results*: 134 consecutive eligible women responded to the in-person paper survey. 55% were partnered, 35.1% had no children, and 48% reported willingness to have children prior to BC diagnosis. Only 3% of patients considered to be able to afford extra expenses. At diagnosis, 44% of women expressed some level of concern about infertility risk. The only factor significantly associated with fertility concern was the desire of having children prior to diagnosis (OR 11.83, p = 0.006). Only 30.6% patients recalled having received information regarding infertility risk from their physicians.

Conclusion: A minority of young women with breast cancer in Mexico is informed about the risk of BC treatment-induced infertility, despite substantial interest. Informing all patients about infertility risk and available options for fertility preservation should be an essential aspect of the supportive care of young women with BC, even in low-middle income countries such as Mexico.

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## 1. Background

Young age, defined as  $\leq$  40 years at the time of diagnosis [1], has been recognized as a predictor of aggressive disease and poor outcomes in patients with breast cancer (BC) [2]. International guidelines recommend the use of systemic treatment in premenopausal women with chemotherapy and/or hormonal therapy

E-mail address: acastrosan@conacyt.mx (A. Castro-Sanchez).

(depending on stage at diagnosis and the expression of hormone receptors and HER2 status), as these therapeutic options improve survival [1,3]. However, they also pose potential risks to premature menopause and infertility, an issue of great importance for young women who have not completed childbearing [4].

In the United States (US), England and other developed countries, the number of live births for women in their 30s and 40s has risen in the past years [5,6]. A similar distribution has been reported in less developed countries such as Mexico, where 25.5% of child births occur in women 30 years or older, according to data from the National Institute of Statistics and Geography (INEGI) [7].

In Mexico, BC among young women represents a significant

 $<sup>\</sup>ast$  Corresponding author. Av. San Fernando #22, Tlalpan, 14080, Mexico City, Mexico.

burden, due to the fact that a very high proportion of the total number of BC patients are diagnosed in their early years, with figures reaching 11%–15% [8,9]. For these young patients, fertility impairment may be a very relevant issue [10], as evidence suggests that young patients with BC experience greater psychological distress and anxiety due to concern for possible future loss of fertility following anticancer treatments [11,12].

In Latin America, no previous studies have addressed the attitudes of young women with BC regarding infertility risk and its contributing factors, or whether these patients are informed at diagnosis about the possible infertility risk and if timely referrals to a fertility specialist occur. The aim of this study was to evaluate the attitudes of young women with BC towards the risk of infertility due to systemic treatment in two referral centers in Mexico.

#### 2. Methods

A cross-sectional study was conducted at the Instituto Nacional de Cancerologia (INCan) in Mexico City and the Breast Cancer Center at Hospital San Jose (HSJ) Tec de Monterrey in Monterrey City, where patients have access to public health services. All women aged 40 years or younger at diagnosis, with newly or previously diagnosed BC that attended clinic from May 2015 to August 2016, were invited to participate.

The survey was administered in-person on paper before or after the clinic visit. The survey included 25 items, adapted from the Fertility Issues Survey of the "Helping Ourselves, Helping Others: the Young Women's Breast Cancer Study" from the Dana-Farber Cancer Institute in Boston, Massachusetts [13]. Additional characteristics, including clinical and pathological variables, were obtained from medical record review. The survey questions were originally translated and back-translated to apply the assessment to Spanish speaking residents in the US. For our current research, we modified the Spanish version minimally for better adaptation to the Mexican population. BC specialists born and raised in Mexico, who speak and write both English and Spanish, reviewed the survey for content comprehension.

Significant differences were determined by Fisher's exact test and Pearson's chi-squared test for categorical variables, and Kruskal-Wallis test for continuous non-parametric variables. A p value of <0.05 was considered statistically significant. Univariate analysis assessed the association between fertility concern (dichotomized as very, somewhat or a little concerned versus not at all concerned) and sociodemographic factors, stage at diagnosis and treatments, and prior fertility-related issues. Variables associated with univariable p value < 0.05 were evaluated in a multivariable logistic regression model using stepwise selection, and variables achieving significance at p < 0.05 were included in the final model. Statistical analyses were performed using SPSS v20.0 (IBM Corporation, 2012).

Study procedures were reviewed and approved by the Institutional Review Boards at INCan and HSJ, and written consent was obtained from all participants before study participation.

## 3. Results

A total of 134 consecutive eligible patients were included in the present study. Mean age at diagnosis was 34.6 years (range 19–40 y) and 50.8% were 35 years or younger at the time of diagnosis. Only 3% of patients considered to be able to afford extra expenses.

At diagnosis, 45.5% were either single, widowed or divorced and 35.1% had no children. Almost half of the patients (47.8%) reported willingness to have children prior to BC diagnosis, while 29.1% desired to have children at the time of the survey. Two patients

(1.5%) were pregnant at time of diagnosis. Table 1 lists the remaining patient and disease characteristics.

Forty-four percent of the patients expressed some level of fertility concern (very, somewhat or a little concerned). Table 2 summarizes the degree of fertility concerns. Fifteen (11.2%) patients reported having difficulties achieving pregnancy prior to cancer diagnosis, and four of them had undergone assisted reproductive techniques.

In a comparative analysis between having or not having children prior to BC diagnosis and level of fertility concerns, 68.1% of women who had no children expressed some level of concern about infertility risk, compared to a smaller proportion of women who already had children (31%) (p < 0.001). Similarly, 81% of the patients who were interested in having future pregnancies prior to BC diagnosis showed some level of concern about infertility risk after systemic treatment in comparison with 6.7% of those who were not interested in future pregnancies (p < 0.001).

The association between socio-demographic/clinical variables and the level of fertility concern is also shown in Table 1. In unadjusted analysis, younger age, not having children prior to diagnosis, desire of having children preceding diagnosis, single status and previous difficulties on achieving pregnancy resulted as significant predictors of fertility concern. After multivariable analysis, the only factor that remained statistically significant was the desire of having children prior to diagnosis (OR 11.83, 95%CI 2.06–67.93, p=0.006).

Thirty (22.4%) patients mentioned that their treatment decision regarding chemotherapy and endocrine therapy was changed due to fertility concerns (Table 3). Of the patients that desired future pregnancies at time of diagnosis, 17.2% were worried about not being able to care for their children in case of cancer recurrence. Of the patients that did not desire future pregnancies, the main reason (20.1%) was that they had completed their family plan prior to cancer diagnosis (Table 4).

Table 5 summarizes our study findings and compares them to data reported in the *Helping Ourselves*, *Helping Others: The Young Women's Breast Cancer Study* [14] and a web-based survey of fertility issues in young women with BC [11], the largest two studies addressing fertility concerns from the Dana Farber Cancer Institute group.

When questioning about the information received by cancer specialists regarding possible fertility impairment secondary to systemic treatment, 41 (30.6%) patients recalled having received information from their physicians. Only one patient underwent fertility preservation treatment through embryo cryopreservation prior to receiving systemic treatment and after being informed of infertility risk by her physician.

#### 4. Discussion

This is the first study describing fertility concerns and receipt of information regarding risk of infertility among young women with BC in Mexico. Findings confirm and expand upon prior work in other populations of young BC survivors regarding concern about the possible loss of fertility [12,15]. Although important factors such as young age, being single, not having children and previous difficulty achieving pregnancies should be asked and considered for referral for fertility preservation strategies, the most important and strongly associated predictor of fertility concern was the desire to have children. This should be highlighted as physicians must inform all young patients about infertility risk and offer preservation options, regardless of marital status and having previous children, emphasizing that this consideration should rely solely on the patients' preferences and not on providers' opinions associated with potential biases.

 Table 1

 Association between fertility concerns and variables of interest.

Variable	Total	Fertility concerned N (%)	Not fertility concerned N (%)	P value
Age in years (median, range)	35, 19-40	33, 19-40	37, 20-40	0.002
Relationship status				
Partner (married or domestic partnership)	73 (54.5)	22 (30.1)	51 (69.9)	< 0.001
No partner (single or widow)	61 (45.5)	37 (60.7)	24 (39.3)	
Socioeconomic status perception				0.644
Enough money for extra expenses	4(3)	1 (25)	3 (75)	
Little money for extra expenses	16 (11.9)	6 (37.5)	10 (62.5)	
Money only to cover necessary expenses	43 (32.1)	22 (51.2)	21 (48.8)	
Not enough money to cover necessary expenses	45 (33.6)	20 (44.4)	25 (55.6)	
Unknown	26 (19.4)			
Stage				
Early (I-IIA)	42 (31.7)	22 (56.4)	17 (43.6)	0.215
Locally advanced (IIB-IIIC)	84 (62.6)	39 (50.6)	38 (49.4)	
Metastatic (IV)	8 (5.7)	6 (85.7)	1 (14.3)	
Mastectomy				
Yes	96 (71.6)	51 (53.1)	45 (46.9)	0.470
No	28 (20.9)	17 (60.7)	11 (39.3)	
Unknown	10 (7.5)			
Chemotherapy	, ,			
Yes	109 (81.3)	60 (55.0)	49 (45.0)	0.717
No	15 (11.2)	8 (53.3)	7 (46.7)	
Unknown	10 (7.5)			
Tamoxifen	, ,			
Yes	86 (64.2)	46 (53.5)	40 (46.5)	0.709
No	44 (32.8)	27 (61.4)	17 (38.6)	
Unknown	4 (3.0)	, ,	, ,	
Prior difficulty on achieving pregnancy				
No	87 (64.9)	54 (62.1)	33 (37.9)	0.017
Yes	15 (11.2)	8 (53.3)	7 (43.7)	
Have not tried	26 (19.4)	8 (30.8)	18 (69.2)	
Unknown	6 (4.5)	,	, ,	
Children prior to diagnosis	` '			
No	47 (35.1)	60 (69.0)	27 (31.0)	< 0.0001
Yes	87 (64.9)	15 (31.9)	32 (68.1)	
Desire of having children prior to diagnosis	` ,	` '	` ,	
Yes	64 (47.8)	52 (81.2)	12 (18.8)	< 0.0001
No	60 (44.8)	4 (6.7)	56 (93.3)	
Not sure	10 (7.5)	3 (30.0)	7 (70.0)	

**Table 2** Fertility concerns.

Degree of concern	N	%
Very concerned	22	16.4
Somewhat concerned	17	12.7
Little concerned	20	14.9
Not concerned at all	75	56.0

**Table 3** Effect of infertility risk on patient treatment decisions.

Treatment decisions	N	%
It did not affect my treatment decisions	104	77.6
I chose to take tamoxifen for less than 5 years	11	8.2
I chose one chemotherapy regimen over another	9	6.7
Rejected endocrine therapy	2	1.5
Other changes	8	6.0

Notably, while fertility concerns had a direct impact on systemic treatment decisions in 22.4% of patients, similar to that reported in other series [11,14], only one patient (0.7%) ultimately pursued fertility preservation, contrasting with the rate reported in other studies which rises from 6 to 10% [14,16]. While low fertility referrals by treating physicians might certainly play an extremely important reason, patients' and physicians' concerns about the safety of future pregnancies following BC diagnosis and treatment

can be another plausible explanation [17]. The fear of increasing risk of recurrence due to pregnancy represented one of the main concerns, demonstrating that this topic deserves further education and awareness. Current data support the safety of pregnancy after BC diagnosis and should not be discouraged anymore [4,18].

This study showed that only 31% of the patients received information by their physicians regarding the risk of infertility prior to starting oncologic treatment, compared to figures previously reported in developed countries that vary from 34 to 72% [12,19]. Despite national and international guidelines recommending that "every patient in fertile age who is candidate for oncologic treatment must be informed about the risk of infertility and options for fertility preservation must be discussed with a specialist" [1,4,19,20], still a minority of patients in our study reported having received appropriate information. In the two studies that served for comparison, the proportion of patients that received infertility risk assessment in higher resource settings was significantly more frequent (see Table 5).

It could be speculated that one of the main reasons for this is a lack of knowledge of attending physicians on the available treatments for fertility preservation, as has been previously reported in developed countries [21,22]. Other reasons might be the lack of knowledge on the effects of systemic therapy on fertility, the concern about the effect of pregnancy on BC prognosis, the high proportion of advanced BC cases in young patients, the concern of physicians of delaying cancer treatment if fertility preservation is pursued, or simply lack of time during medical visits to explain

**Table 4** Concerns about future pregnancies at time of diagnosis.

Reasons	Desire future pregnancies		Do not desire future pregnancies	
	N	%	N	%
Being unable to care for children in case of cancer recurrence	23	17.2	10	7.5
Having a child with greater possibilities of developing cancer	10	7.5	8	6.0
Possibility of increasing risk of recurrence due to pregnancy	8	6.0	8	6.0
Other reasons	8	6.0	20	14.9
Finished having children prior to breast cancer diagnosis	_	_	27	20.1
Two of the previous reasons	3	2.1	3	2.1

**Table 5**Comparative results between the present study findings and two of the largest studies addressing fertility concerns.

	Web-Based Survey of Fertility Issues in Young Women with Breast Cancer (2004) [11]	Prospective Study of Fertility Concerns and Preservation Strategies in Young Women With Breast Cancer (2014) [14]	Fertility concerns among breast cancer patients in Mexico (2017)
Population	N = 657	N = 620	N = 134
	32.9 years	37 years	34.6 years
	70% married or living as married	78% married	55% married or partnered
	60% can afford "special things"	50% financially comfortable	3% can afford extra expenses
	66% < 35y	37% < 35y	50.8% < 35y
Stage at diagnosis	0, 10%; I, 27%; II, 47%; III, 13%	0, 8%; I, 36%; II, 43%; III, 13%	0, 3.3%; I, 8.1%; II, 52.8%; III, 30.1%;
			IV, 5.7%
Desired future children	56%	37%	48%
Had a live birth at diagnosis	48%	66%	65%
Discussed fertility issues with their physicians	72%	68%	31%
Some degree of concern about fertility at the time of diagnosis	73%	51%	44%
Concerns about fertility affected their treatment decisions	29%	26%	22%
Association between fertility concerns and variables of interest	Wish for children/more children $(p < 0.0001)$ ; number of prior pregnancies $(p = 0.01)$	Age $<35y$ (p $<0.001$ ); married (p $<0.001$ ); no children (p $<0.001$ ); no previous pregnancy (p $<0.001$ ); no mastectomy (p $<0.001$ )	Desire of having children prior to diagnosis $(p < 0.0001)$
Used fertility preservation strategies	- "	10%	0.7%

these effects and possible options.

Also, patients' socioeconomic status might be a limiting factor in discussion and referrals for fertility preservation. These procedures often represent an out-of-pocket expense for patients, particularly in limited settings with income inequities and highly variable access to reproductive care, as reported in other low-middle income countries such as Puerto Rico [23]. The costs of oocyte, embryo or ovarian tissue cryopreservation are usually high, in addition to the processes of ovarian stimulation, follicular aspiration, and in vitro fertilization, Luteinizing hormone-releasing hormone (LHRH) analogues are a less expensive option that is now covered by some national healthcare systems [24]. Although the data on subsequent pregnancies remains limited, this option proved to aid in ovarian function preservation [25]. Unfortunately, in Mexico, LHRH analogues are not covered by the healthcare system, as the other fertility preservation strategies. Data in Table 5 highlights the differences between the patients' socioeconomic perceptions in our population and the US studied sample: only 3% of Mexican patients can afford extra expenses compared to 50-60% of young women living in resourceful settings that considered themselves as financially comfortable.

Finally, BC patients in Mexico may lack appropriate and sufficient information regarding ovarian failure and infertility, due to inadequate communication with their healthcare providers, as well as deficiency of written and electronic information on specific issues faced by young patients, in general, including not only fertility preservation, but genetic counseling, and treatment side effects, as shown in previous studies [26,27]. The provision of written

materials and web-based decision aids have improved patient access to fertility discussions and fertility preservation [28,29], and efforts should be made to develop and provide such resources routinely in diverse settings in native language for young patients.

The main weakness of our study relies on its cross-sectional design. Most of the patients were surveyed one to five years after diagnosis (median time: 2 years); therefore, it is possible that some patients did not accurately recall if they received information on aspects related to fertility. Additionally, the process of BC diagnosis and treatment is usually emotionally challenging and represents a moment in which patients might not acknowledge all the information provided. Also, the socioeconomic status of our patients must be taken into account, as their medical coverage generally does not include assisted reproductive techniques, the number of patients with access to such procedures might be limited.

However, our study has several strengths. The recruitment of patients took place in two reference centers for BC, where the prevalence of young women is 15% [30]. Also, this study represents the first effort in Mexico to evaluate fertility concerns in young BC patients. Furthermore, we applied a previously used survey to investigate similar issues, which was adapted and validated for Spanish speaking Mexican patients.

International efforts have been made to routinely evaluate patients' interest on future fertility, to ensure that they receive adequate information on possible infertility risk, and to guarantee timely referrals to fertility specialists through comprehensive programs for young women with BC [1,3]. In fact, the integration of dedicated programs for young BC patients to clinical care has been

associated with a higher frequency of fertility preservation referrals [31]. The "Joven y Fuerte: Programa para la Atención e Investigación de Mujeres Jóvenes con Cáncer de Mama" is the first initiative in Mexico that seeks this purpose and is active at INCan and HSJ since 2014. Since the incorporation of this Program, 18 patients have been referred for fertility preservation, some of them with partial or total costs coverage through inter-institutional agreements and/or external funding. It is intended to replicate this initiative in other nationwide reference centers in the near future.

## 5. Conclusion

Almost half of the studied population had interest in a subsequent pregnancy before BC diagnosis, but only one patient underwent a fertility preservation procedure. Even though one of the most frequent adverse effects of anticancer treatments is secondary ovarian failure, less than one third of patients recalled receiving this information. Dedicated programs for young women with BC may improve the frequency of fertility discussion and preservation referrals by allowing the delivery of standardized information to patients, promoting local alliances between oncology and reproductive centers, and systematically addressing barriers including costs for underserved patients. Informing all patients about infertility risk and available options for fertility preservation should be essential aspects of their supportive care, even in low-middle income countries such as Mexico, where socioeconomic barriers must be overcome to pursue this right.

#### **Conflict of interest statement**

The authors have declared that no completing interest exists.

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