


## Fertility and ovarian function preservation in young women with breast cancer: A joint analysis of the Joven & Fuerte and PREFER prospective studies

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### ABSTRACT

**Background:** Potential infertility and premature ovarian insufficiency represent notable concerns for young women with breast cancer (YWBC) undergoing chemotherapy. Cryopreservation techniques and temporary ovarian suppression with GnRH agonists (GnRHa) can be offered for fertility preservation (FP) and/or ovarian protection. This joint analysis of the Joven & Fuerte and PREFER multicenter prospective studies compared the uptake of these strategies and associated factors among Mexican and Italian YWBC.

**Methods:** Females  $\leq 40$  years diagnosed with non-metastatic BC from 2014 to 2019, who were offered FP strategies before (neo)adjuvant chemotherapy were included. Uptake of GnRHa for ovarian protection and cryopreservation procedures and reasons for their non-utilization were examined.

**Results:** Among 485 patients (74 % from Mexico; 26 % from Italy), cryopreservation techniques were used in 8 % of Mexican patients and 25 % of Italian patients ( $p < 0.001$ ). Methods in Mexico and Italy, respectively, comprised oocyte (50 % and 87 %), embryo (53 % and 0 %), and ovarian tissue (0 % and 16 %) cryopreservation. GnRHa were used in 98 % of Italian patients and 6 % of Mexican patients. Cryopreservation uptake was associated with younger age (OR 1.2, 95 %CI 1.1–1.2), childlessness (OR 21.8, 95 %CI 10.0–47.6), stage I-II BC (OR 3.1, 95 %CI 1.5–6.3), private healthcare in Mexico (OR 3.0, 95 %CI 1.1–8.1), and unpartnered status in Italy (OR 5.4, 95 %CI 2.2–13.2).

**Conclusion:** FP and ovarian protection uptake were markedly higher in Italy than Mexico, possibly reflecting divergent social and healthcare contexts, though cryopreservation remained underutilized in both countries. Improved access to oncofertility services is warranted to provide comprehensive care aligned with the personal needs and life plans of YWBC.

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## 1. Introduction

Young women with breast cancer (YWBC) comprise a distinct patient population with unique physical and psychosocial needs [1]. The incidence of breast cancer (BC) in this group represents approximately 5 % of all new BC cases per year in countries such as Italy, while in more limited-resource settings like Mexico it accounts for up to 15 % of cases [2]. BC during reproductive years poses significant personal and public health challenges. Potential premature ovarian insufficiency and infertility secondary to chemotherapy-related gonadotoxicity are notable concerns for YWBC [1,3]. Therefore, national and international BC guidelines recommend oncofertility counselling for all women of childbearing age, prior to beginning any oncological treatment [1,4–8]. This counselling is crucial to inform patients about the fertility-related effects of cytotoxic treatments and to discuss fertility preservation and ovarian protection options, emphasizing their efficacy and safety [1,9,10].

The standard fertility preservation (FP) strategies for YWBC, performed before the administration of systemic anticancer therapy, are oocyte, embryo, or ovarian tissue cryopreservation [5,11,12]. Temporary ovarian function suppression with a gonadotropin-releasing hormone agonist (GnRHa) during chemotherapy is recommended to protect ovarian function in YWBC. GnRHa can be used jointly with cryopreservation procedures or separately when these techniques are not feasible [4,5,11–14].

Despite being guideline-endorsed, a considerable number of YWBC do not receive oncofertility counselling; thus, further efforts to increase awareness and access to FP and ovarian protection options are necessary [15,16]. A potential gap may be related to limited discussion of fertility concerns and preservation options between oncologists and patients. For example, in Mexico only 31 % of YWBC reported having received information about the risk of treatment-induced infertility, compared to higher rates in other developed countries including Italy [17–20]. Furthermore, although nearly half of YWBC may desire a future pregnancy, many face concerns about its safety, especially regarding recurrence risk [21].

Referral to oncofertility care requires careful consideration of patient's characteristics and priorities, given that the choice to undergo cryopreservation procedures or ovarian protection may depend on various aspects. Some examples include age, ovarian reserve, partnership status, *BRCA* status, clinical stage, treatment plan, and time available before starting treatment [11,22].

This joint analysis of the two prospective studies Joven & Fuerte and PREFER compares the uptake of fertility and ovarian preservation methods and associated factors among YWBC from Mexico and Italy. This information may provide a more comprehensive understanding of the personal, financial, or cultural factors influencing the use of cryopreservation and ovarian protection strategies, with the ultimate goal of enhancing access to oncofertility care in YWBC.

## 2. Methods

### 2.1. Joven & Fuerte – study description

Joven & Fuerte is an observational, prospective, multicenter study established in 2014 in three major BC referral centers in Mexico, including both public and private healthcare representation. Its fertility-focused component is aimed at identifying the needs and access to available FP methods including oocyte or embryo cryopreservation and GnRHa for ovarian protection [24].

Once a young woman is diagnosed with BC, a patient navigator provides them education about the risk of premature ovarian insufficiency with potential infertility and early menopause due to oncologic treatments. The navigator also assists in making prompt referrals to comprehensive oncofertility counselling for those interested in cryopreservation procedures. This navigation service is specifically offered

to patients enrolled in Joven & Fuerte, as patient navigation is not routinely provided in healthcare institutions in Mexico. To enhance access to cost-intensive preservation strategies, Joven & Fuerte has established a network with assisted-reproduction units, which offer cryopreservation techniques at reduced rates for patients with low socioeconomic status. Additionally, government assistance with the costs of cryopreservation procedures has been obtained for a limited number of underserved patients in the program. As for GnRHa for ovarian protection during chemotherapy, their prescription is independent from Joven & Fuerte and depends on the oncologists' consideration and decision. Of note, while GnRHa for ovarian protection are reimbursed by private insurances in some cases, they are seldom covered by public healthcare in Mexico.

### 2.2. PREFER – study description

PREFER (PREGnancy and FERtility) is an observational, prospective, multicenter cohort study conducted in 34 Italian institutions that started recruitment in November 2012, under the coordination of IRCCS Ospedale Policlinico San Martino in Genoa [15]. Its fertility-related objectives encompass investigating young patients' needs and choices of ovarian protection and/or cryopreservation techniques at the time of BC diagnosis [15].

A specific algorithm was developed to provide adequate oncofertility counselling, which should be offered to all YWBC in accordance with the national FP guidelines of the Italian Association of Medical Oncology (AIOM) [7]. All young patients with non-metastatic BC are informed by the oncologist about the risk of premature ovarian insufficiency, which may lead to potential infertility and early menopause secondary to chemotherapy-induced gonadotoxicity. Patients are also educated about the available strategies to counteract these potential outcomes. For patients  $\leq 40$  years who express a desire to preserve fertility and/or ovarian function, both comprehensive reproductive counselling at an oncofertility unit to access cryopreservation procedures and temporary ovarian suppression with GnRHa during chemotherapy are proposed. Depending on the patient's age and the time available before starting oncological treatments, options for FP may include oocyte or ovarian tissue cryopreservation. Embryo cryopreservation in women with cancer is forbidden by law. In Italy, both GnRHa for ovarian function protection and cryopreservation techniques are covered by the public healthcare system [23].

### 2.3. Joint and comparative analysis

The present work is a joint analysis of these two prospective studies conducted in Mexico and Italy. Both studies aimed to explore fertility-related needs and optimize care by providing early referrals to FP or ovarian protection strategies at diagnosis as needed. Since they are almost overlapping in terms of objectives, inclusion criteria, and methods, they allowed for a comprehensive and in-depth analysis of the similarities and differences existing between the two countries. To homogenize eligibility criteria, this analysis included patients enrolled from 2014 to 2019 who were  $\leq 40$  years at diagnosis of invasive non-metastatic BC and who were treated with (neo)adjuvant chemotherapy. In the case of the PREFER study, only the two centers with largest number of enrolled patients were included in this analysis in order to analyze data from a similar number of centers as the Joven & Fuerte study.

The Joven & Fuerte study was approved by Research and Ethics committees of Instituto Nacional de Cancerología in May 2014 and the TecSalud – Tecnológico de Monterrey hospitals in March 2015. The PREFER study was approved by the Ethics Committee of the coordinating center in November 2012 and is registered on the [ClinicalTrials.gov](https://www.clinicaltrials.gov) website (NCT02895165) [15]. In both cohorts, all patients provided their informed consent to participate.

To compare patients' uptake of cryopreservation procedures and

GnRHa for ovarian protection between the two countries and factors associated with use of these strategies, data included in this analysis consisted of patient-reported demographic characteristics and physician-recorded clinical information collected at the time of enrolment and up to one-year follow-up. Patients' uptake of cryopreservation procedures and GnRHa for ovarian protection and reasons for their non-utilization were examined. Variables of particular interest were age, menopausal status, parity, partnership status, medical affiliation, desire for future offspring, clinical stage, histological BC subtype, *BRCA* status, and timing of chemotherapy (i.e. neoadjuvant vs adjuvant).

Descriptive statistics were employed to analyze patients' demographic and clinicopathologic characteristics, as well as the use of GnRHa for ovarian protection purposes and cryopreservation techniques. Chi-squared, Fisher's exact, and Wilcoxon tests were used to compare patients' characteristics within and across cohorts. Logistic regression was conducted to calculate the odds ratio (OR) and 95 % confidence interval (95 %CI) of undergoing a cryopreservation procedure. An OR >1 indicated a higher likelihood, while an OR <1 indicated a lower likelihood of uptake of a cryopreservation procedure. A  $p < 0.05$  was considered significant. Statistical analyses were performed using SAS 9.4 (SAS Institute).

### 3. Results

In total, 485 YWBC were included: 361 (74 %) from the Joven & Fuerte study and 124 (26 %) from the PREFER study (Fig. 1).

Patients' baseline characteristics per cohort are detailed in Table 1. The median age at diagnosis of the joint cohorts was 36 years (IQR 32–38). Patients were covered by public healthcare in 88 % of cases in Mexico and 100 % of cases in Italy. A higher proportion of Mexican patients had a partner compared to Italian ones (65 % vs 59 %,  $p = 0.04$ ). Patients' median number of children at diagnosis was also higher in Mexico than in Italy (2 [IQR 1–3] vs 1 [IQR 0–2],  $p < 0.001$ ). Mexican patients were more often diagnosed with stage III BC (41 % in Mexico vs 19 % in Italy,  $p < 0.001$ ) and received neoadjuvant chemotherapy (53 % in Mexico vs 40 % in Italy,  $p = 0.01$ ). In contrast, Italian patients more frequently had hormone receptors (66 % in Mexico vs 76 % in Italy,  $p = 0.04$ ) or HER2 positivity (22 % in Mexico vs 36 % in Italy,  $p = 0.002$ ).

Out of 367 (76 %) patients tested for germline *BRCA* pathogenic or likely pathogenic variants, 78 (21 %) were *BRCA* carriers (22 % of those tested in the Mexican cohort and 21 % of those in the Italian cohort) and 289 (79 %) were *BRCA* wild type. The rest of the population (24 %) did not undergo genetic testing.

Uptake of cryopreservation techniques and GnRHa for ovarian function protection was significantly different across cohorts (Fig. 2). Overall, only a minority of the patients in both cohorts opted for a cryopreservation procedure, representing 13 % of the total patients: 30 (8 %) in Mexico and 31 (25 %) in Italy ( $p < 0.001$ ). Only 21 (6 %) Mexican patients used GnRHa compared to nearly all Italian patients ( $n = 121$ , 98 %).

Cryopreservation methods comprised oocyte (4 % in Mexico and 22 % in Italy), embryo (4 % in Mexico and 0 % in Italy), and ovarian tissue cryopreservation (0 % in Mexico and 4 % in Italy) (Fig. 3). Of note, 1 patient in Mexico underwent both oocyte and embryo cryopreservation, and 1 patient in Italy opted for both oocyte and ovarian tissue cryopreservation.

Not undergoing FP or ovarian protection was mainly due to lack of interest -including having already had children- (50 % in the Mexican cohort and 45 % in the Italian cohort), urgency to start treatment (4 % Mexico and 6 % in Italy), and other personal reasons (3 % in Mexico and 5 % in Italy).

In both cohorts, undergoing a cryopreservation method was associated with younger age (OR 1.2, 95 %CI 1.1–1.2), childlessness (OR 21.8, 95 %CI 10.0–47.6), and stage I-II BC (OR 3.1, 95 %CI 1.5–6.3). In the Mexican cohort, private healthcare coverage (OR 3.0, 95 %CI 1.1–8.1) was also associated, while in the Italian cohort, unpartnered status (OR 5.4, 95 %CI 2.2–13.2) was significant. Predictors of cryopreservation uptake per country and in the total cohort are detailed in Table 2.

Of the 331 patients with hormone receptor-positive BC, 50 (15 %) underwent a cryopreservation technique: oocyte ( $n = 37$ ), embryo ( $n = 11$ ), and ovarian tissue cryopreservation ( $n = 4$ ) (2 patients accepted 2 types of techniques). In comparison, 11/154 (7 %) patients with hormone receptor-negative BC used a cryopreservation method: oocyte ( $n = 5$ ), embryo ( $n = 5$ ), and ovarian tissue cryopreservation ( $n = 1$ ).

In the case of *BRCA* carriers ( $n = 78$ ), 7 used a cryopreservation technique. Specifically, 4 chose oocyte, 2 embryo, and 2 ovarian tissue cryopreservation (one patient accepted two types of techniques).

### 4. Discussion

This joint and comparative analysis of two similar prospective studies in Mexico and Italy observed significant differences in the uptake of cryopreservation procedures and GnRHa for ovarian protection by each population of YWBC, which may be suggestive of the different backgrounds of these countries. While cryopreservation rates were low overall in both cohorts, access to GnRHa was particularly limited in

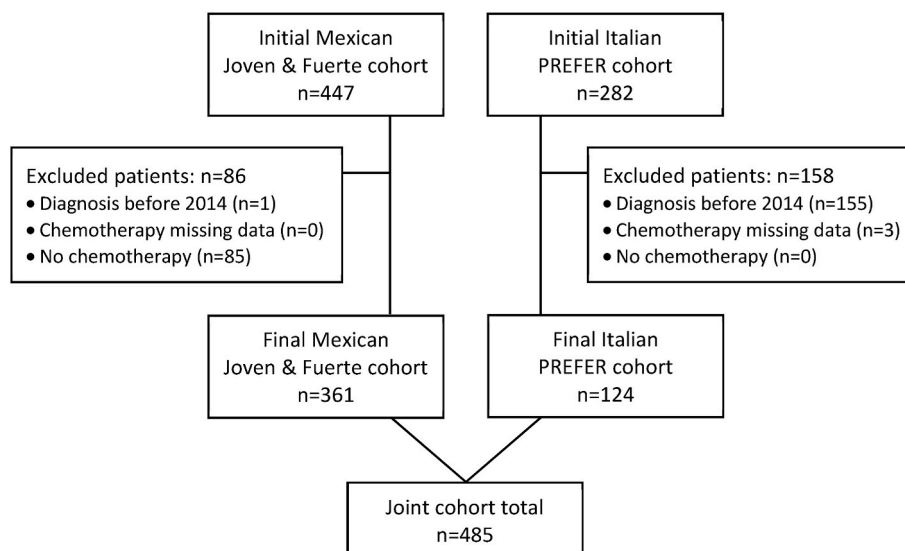


Fig. 1. Flow diagram of participants.

**Table 1**  
Patients' baseline characteristics.

Characteristic	Total n = 485 (%)	Mexican cohort n = 361 (%)	Italian cohort n = 124 (%)	p
Median age, years (IQR)	36 (32–38)	36 (32–38)	35 (32–38)	0.815
Age distribution				0.198
≤30	86 (17.7)	63 (17.4)	23 (18.5)	
31-35	152 (31.3)	106 (29.4)	46 (37.1)	
36-40	247 (51.0)	192 (53.2)	55 (44.4)	
Type of healthcare insurance				NA
Public	440 (90.7)	316 (87.5)	124 (100.0)	
Private	34 (7.0)	34 (9.4)	0 (0.0)	
Missing	11 (2.3)	11 (3.0)	0 (0.0)	
Median number of children (IQR)	1 (0–2)	2 (1–3)	1 (0–2)	<0.001
Partnership status				0.041
No partner	157 (32.4)	106 (29.4)	51 (41.1)	
Partner	309 (63.7)	236 (65.4)	73 (58.9)	
Missing data	19 (3.9)	19 (5.2)	0 (0.0)	
BRCA status				0.765
Pathogenic/likely pathogenic variant	78 (16.1)	57 (15.8)	21 (16.9)	
No pathogenic/likely pathogenic variant	289 (59.6)	216 (59.8)	73 (58.9)	
Not tested/unknown	118 (24.3)	88 (24.4)	30 (24.2)	
BC clinical stage				<0.001
I	68 (14.0)	38 (10.5)	30 (24.2)	
II	247 (50.9)	176 (48.8)	71 (57.3)	
III	170 (35.1)	147 (40.7)	23 (18.5)	
Hormone receptor status				0.036
Negative	154 (31.7)	124 (34.3)	30 (24.2)	
Positive	331 (68.3)	237 (65.7)	94 (75.8)	
HER2 status				0.002
Negative	359 (74.0)	280 (77.6)	79 (63.7)	
Positive	126 (26.0)	81 (22.4)	45 (36.3)	
Timing of chemotherapy				0.010
Neoadjuvant	240 (49.5)	191 (52.9)	49 (39.5)	
Adjuvant	245 (50.5)	170 (47.1)	75 (60.5)	

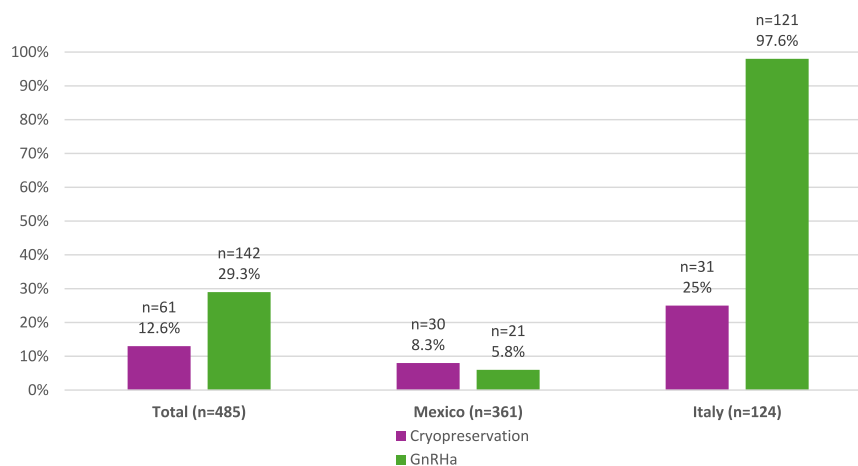
IQR: interquartile range; NA: not applicable.

**Mexico.**

Mexico and Italy are two countries with cultural, economic, social, educational, and health system differences. These characteristics may influence healthcare decisions, especially regarding cost-intensive treatments and techniques which are not equally covered by the public and private healthcare policies in each country. In this case, a significant difference concerns the use of cryopreservation techniques and GnRH $\alpha$ . In the Mexican cohort, less than 10 % of YWBC underwent a

cryopreservation method. Although in Italy this percentage was higher, the uptake of these procedures was still relatively low (25 %). Noteworthy, in Italy cryopreservation techniques are fully funded by the National Health Service which provides healthcare to all Italian citizens and residents. In contrast, the Mexican health system, which is fragmented into diverse public and private insurance plans, does not cover these strategies.

The most frequently used technique by patients in the Italian cohort



**Fig. 2.** Uptake of cryopreservation techniques for fertility preservation and GnRH $\alpha$  for ovarian protection.

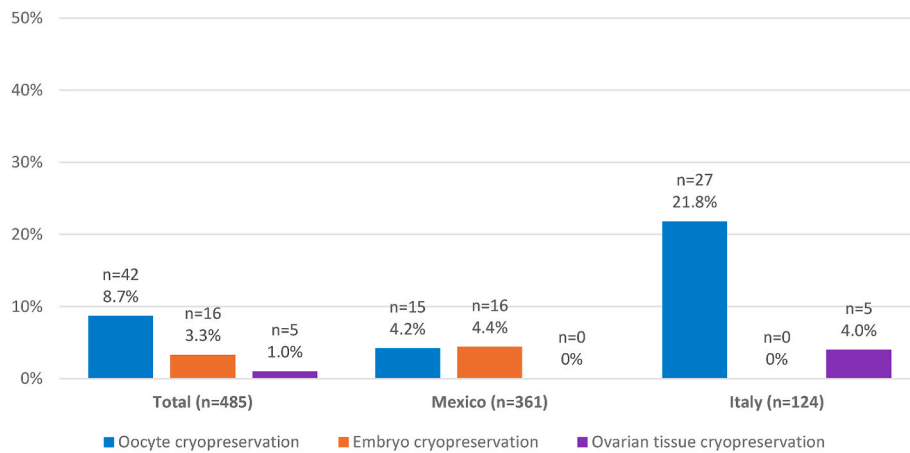


Fig. 3. Uptake of each type of cryopreservation technique.

Table 2  
Predictors of use of a cryopreservation technique.

Variable	Total n = 485 (%)		Mexican cohort n = 361 (%)		Italian cohort n = 124 (%)	
	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p
Age at diagnosis (inverse)	1.16 (1.09–1.23)	<0.001	1.13 (1.04–1.22)	0.003	1.25 (1.12–1.39)	<0.001
Partnership status		<0.001		0.070		<0.001
Partner	1 (ref)		1 (ref)		1 (ref)	
No partner	3.41 (1.94–5.97)		2.06 (0.94–4.50)		5.39 (2.21–13.15)	
Number of children		<0.001		<0.001		<0.001
≥1	1 (ref)		1 (ref)		1 (ref)	
0	21.82 (10.00–47.63)		19.88 (7.26–54.45)		16.97 (4.79–60.06)	
Clinical stage		<0.001		0.046		0.006
III	1 (ref)		1 (ref)		1 (ref)	
II	2.21 (1.05–4.66)		1.62 (0.67–3.93)		2.81 (0.59–13.36)	
I	7.15 (3.15–16.24)		3.92 (1.32–11.63)		9.19 (1.82–46.34)	
Hormone receptor status		0.016		0.091		0.231
Negative	1 (ref)		1 (ref)		1 (ref)	
Positive	2.31 (1.17–4.58)		2.22 (0.88–5.57)		1.91 (0.66–5.53)	
HER2 status		0.110		0.902		0.238
Negative	1 (ref)		1 (ref)		1 (ref)	
Positive	1.60 (0.90–2.83)		1.06 (0.44–2.56)		1.65 (0.72–3.77)	
Timing of chemotherapy		0.002		0.067		0.076
Neoadjuvant	1 (ref)		1 (ref)		1 (ref)	
Adjuvant	2.41 (1.36–4.27)		2.06 (0.95–4.46)		2.27 (0.92–5.59)	
Healthcare insurance		NA		0.011		NA
Public	NA		1 (ref)		NA	
Private	NA		3.01 (1.12–8.07)		NA	

OR: odds ratio; 95 % CI: 95 % confidence interval; NA: not applicable.

was oocyte cryopreservation (22 %), while in Mexico the rates of oocyte and embryo cryopreservation were 4 % each. In Italy, 4 % of patients opted for ovarian tissue cryopreservation, a technique not available in Mexico until 2019, which is why no Mexican patients in this analysis underwent this strategy. Conversely, embryo cryopreservation is permitted in Mexico, whereas this procedure is prohibited by Italian law 40/2004 [25].

A notable contrast was also observed regarding the use of GnRHα for ovarian function protection: only 6 % of Mexican patients received this strategy compared to 98 % of Italian patients. This striking difference is likely related to the different prescription practices and reimbursement policies for this drug in the two countries. In Italy, the cost of GnRHα is covered by the National Health Service, making it more accessible [7]. In Mexico, patients affiliated to the public healthcare system and some with private insurance must usually bear the full cost of the drug as out-of-pocket expenses. This can lead to possible financial barriers and

lower access especially for patients with public coverage and even among those with private insurance (0.7 % of the population in Mexico) [26]. Likewise, lack of physician awareness of the indication of GnRHα for ovarian function protection can be a relevant barrier in this country, where almost one fourth of physicians wrongly believe that GnRHα are detrimental to the prognosis of YWBC [27]. Considering that GnRHα prescription relies completely on the oncologist’s recommendation, it is essential to improve physicians’ information about the recommended use of this agent for ovarian protection and not only for FP.

When evaluating patient-reported reasons for not undergoing FP or ovarian protection, having already had children accounted for 50 % of the Mexican cohort. In this regard, it is relevant to consider that the age of Mexican women at first pregnancy is markedly lower compared to Italian women (21 vs 31 years) [28,29]. Additionally, young Mexican patients in this study had double the average number of children of the Italian population (2 vs 1) at the time of BC diagnosis. In Mexico, the

global fertility rate has exhibited a decreasing trend, from an average of 2.21 children per woman in 2014, to 2.07 in 2018, to 1.60 in 2023 [30]. Fertility rate in Italy is even lower, with an average of 1.4 children per woman in 2014 that declined to 1.3 in 2019, being among the lowest in Europe [31].

The second most frequent reason for non-utilization of FP or ovarian protection strategies in both cohorts was related to the urgency of starting oncologic treatment. Patients often refer fear of delaying treatment initiation as a consequence of undergoing cryopreservation procedures [32–34]. This finding reinforces the need for oncologists to be appropriately informed of the safety of FP techniques in order to reassure patients about the possibility of choosing these options when the histological and biological characteristics of the tumor allow it [35, 36]. In patients undergoing oocyte or embryo cryopreservation, in order to prevent treatment delays, “random start” protocols allow initiation of ovarian stimulation at any cycle phase and have been demonstrated to be effective [37–39]. Otherwise, ovarian tissue cryopreservation could be proposed, considering that this method can be performed immediately after diagnosis without the need for the two-week ovarian stimulation [5,38].

In this study, factors associated with the uptake of cryopreservation strategies were younger age, childlessness, and earlier-stage BC, as well as private healthcare coverage in Mexico and unpartnered status in Italy. Previous reports have observed that clinicians may be more likely to have FP discussions depending on certain patient characteristics such as age and parity [40–42], and that these same factors can impact the likelihood of pursuing FP [42]. Similarly, patients’ decision to undergo cryopreservation can be importantly influenced by the cost of these procedures, which may be related to the finding in the Mexican cohort where private insurance (mainly held by middle/higher-income patients) was associated with a higher uptake of FP [44,45]. In contrast, other studies did not find an association between clinical stage and the decision to undergo FP [43,46]. Certainly, complete oncofertility counselling should be provided to all YWBC, ensuring that these discussions are not determined by personal assumptions about patients’ needs or preferences. However, it may be worthwhile for oncologists to identify patients with specific characteristics that might particularly benefit from FP or ovarian protection options.

Some considerations should be acknowledged when interpreting the present analysis. Regarding the generalizability of the results, it must be recognized that the Joven & Fuerte and the PREFER studies have established specific processes to favour young patients’ access to oncofertility information and preservation techniques. Consequently, the studied population may have a higher uptake of FP strategies compared to other patients in settings where these types of initiatives are not available. Another important consideration is that it was not possible to explore the factors associated with patients’ uptake of GnRHα for ovarian function protection, given that nearly all YWBC in the Italian study and only a minority of those in the Mexican cohort received this strategy.

As main strengths of this analysis, it should be highlighted that it evaluates data from two of the largest multicenter prospective cohorts of YWBC, providing valuable insights into oncofertility aspects among patients from two different countries. Additionally, it is the first comparative analysis assessing the uptake of ovarian and FP techniques and the main reasons for non-utilization in contrasting contexts. Hence, these findings may contribute to improve knowledge in this field among both specialists and patients as well as to strengthen oncofertility networks to benefit a wider proportion of YWBC.

## 5. Conclusion

This comparative analysis of two prospective studies in Mexico and Italy revealed that a significant distinct proportion of YWBC underwent fertility and ovarian function preservation techniques, even though cryopreservation rates were low in both countries. These disparities

likely reflect the different social and healthcare contexts in each country. Overall, increased access to FP strategies for interested patients is necessary in both Mexico and Italy. Oncofertility services could be strengthened by expanding the establishment of well-coordinated onco-reproductive pathways with access to trained specialists in this field. Likewise, offering coverage or assistance for ovarian protection and cryopreservation options could be key in boosting access for all interested patients, particularly in the Mexican population. This way, it will be possible to provide comprehensive care for YWBC according to their personal needs and life plans.

## CRedit authorship contribution statement

**Fernanda Mesa-Chavez:** Writing – original draft, Visualization, Investigation, Data curation. **Maria Grazia Razeti:** Writing – original draft, Visualization, Investigation, Data curation. **Eva Blondeaux:** Writing – review & editing, Formal analysis. **Alejandra Platas:** Writing – review & editing, Investigation. **Virginia Delucchi:** Writing – review & editing, Formal analysis. **Alan Fonseca:** Writing – review & editing, Investigation. **Valeria Fontana:** Writing – review & editing, Investigation. **Marlid Cruz-Ramos:** Writing – review & editing, Investigation. **Paola Anserini:** Writing – review & editing, Investigation. **Manuel Rolando Gracia Garza:** Writing – review & editing, Investigation. **Edoardo Chiappe:** Writing – review & editing, Investigation. **Alejandro Mohar:** Writing – review & editing, Investigation. **Laura Orlando:** Writing – review & editing, Investigation. **Paula Cabrera-Galeana:** Writing – review & editing, Investigation. **Saverio Cinieri:** Writing – review & editing, Investigation. **Enrique Bargallo-Rocha:** Writing – review & editing, Investigation. **Lucia Del Mastro:** Writing – review & editing, Investigation. **Cynthia Villarreal-Garza:** Writing – review & editing, Supervision, Conceptualization. **Matteo Lambertini:** Writing – review & editing, Supervision, Investigation, Conceptualization.

## Consent to participate

All participants provided written informed consent prior to their inclusion in the Joven & Fuerte and PREFER studies.

## Ethical considerations

The Joven & Fuerte study was approved by the Instituto Nacional de Cancerología Research Ethics Committee (approval no. 014/013/OMI) on May 14, 2014, and by the School of Medicine of Tecnológico de Monterrey Research Ethics Committee (approval no. P000040) on March 26, 2015. The PREFER study was approved by the IRCCS Ospedale Policlinico San Martino Research Ethics Committee (approval no. 001377) on November 23, 2012, and by the Perrino Hospital Research Ethics Committee (approval no. 26399) on October 23, 2014.

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## Declaration of conflicting interest

Matteo Lambertini reports advisory role for Roche, Lilly, Novartis, AstraZeneca, Pfizer, Seagen, Gilead, MSD, Pierre Fabre, Menarini and Exact Sciences; receiving speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Ipsen, Menarini and AstraZeneca; receiving travel grants from Gilead, Roche, and Daiichi Sankyo; receiving research funding (to his institution) from Gilead; and having nonfinancial interests as a member of the national council of the

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### Data availability

The data that support the findings of this study are available from the authors upon reasonable request and if ultimately allowed by local Ethic Committees.

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