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# VIABLE OPTIONS FOR FERTILITY PRESERVATION IN BREAST CANCER PATIENTS: A FOCUS ON LATIN AMERICA

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## ABSTRACT

Thanks to the improved survival outcomes observed in recent years, a growing attention has been given to the quality of life issues faced by young women with breast cancer such as fertility preservation and concerns related to future pregnancies. However, several challenges remain for young women with breast cancer considering undergoing fertility preservation strategies. Further specific issues on this regard should be taken into account in Latin America, where patients and physicians face particular barriers that hinder the routine adoption of this practice. Hence, further efforts are needed to overcome these deficiencies and improve the correct referral of breast cancer patients to fertility preservation strategies.

The aim of the present review is to focus on the risk of anticancer treatment-related premature ovarian failure and infertility in young breast cancer patients, to summarize the current knowledge on the available options for fertility preservation, and to discuss the safety issues of pregnancy in breast cancer survivors. Furthermore, this review aims to highlight the specific clinical challenges in this field encountered by healthcare providers and young breast cancer patients from Latin American countries.

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**Key words:** Breast cancer. Fertility preservation. Premature ovarian failure. Latin America. Young women.

## INTRODUCTION

Among young women of reproductive age, breast cancer is the most commonly diagnosed malignancy<sup>1</sup>. In Latin America, the mean age at diagnosis of breast cancer is approximately 10 years younger than in the United States of America (USA)<sup>2</sup>. In this region, the proportion

of breast cancers arising in premenopausal women on the total incident cases is substantially higher (average 47.3%) as compared to more developed countries (average 18.5%)<sup>3</sup>. Furthermore, while in the USA 5% of the new breast cancer cases are diagnosed in patients under the age of 40, in Latin America the rate of breast cancer in young women reaches 10-15%<sup>2</sup>. Thus, breast cancer

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among young Latin American patients represents a growing burden throughout the region.

Personalized approaches are needed to manage the specific age-associated needs of young women with breast cancer in terms of both optimal anticancer treatments and other crucial quality of life issues<sup>4</sup>. Anticancer therapies can be associated with important long-term negative consequences such as the risk of developing impairment of fertility and premature ovarian failure (POF)<sup>5</sup>. As shown in the “Helping Ourselves, Helping Others: The Young Women’s Breast Cancer Study” conducted in the USA, approximately half of the young women with newly diagnosed breast cancer are worried about the possible treatment-related loss of fertility and ovarian function<sup>6</sup>. These concerns can be associated with important psychosocial distress and might impact the decision on the proposed anticancer treatments<sup>6</sup>. Similar findings have also been observed in young patients from more resource-limited societies. A recent survey conducted in two referral centers in Mexico showed that, at the time of diagnosis, 44% of young breast cancer patients expressed some level of concern about the risk of treatment-related infertility<sup>7</sup>. This study reported that the only significant predictor of infertility concern was the desire for having children preceding diagnosis<sup>7</sup>.

Current guidelines on fertility preservation in cancer patients highlight the importance of informing all patients diagnosed during their reproductive years about the possible risk of treatment-related POF and infertility, and then to discuss the different available options for fertility preservation with interested patients<sup>8,9</sup>. Oncofertility counseling should now be considered as part of routine clinical practice and represents a key moment during the first medical consultation with newly diagnosed young patients<sup>10,11</sup>. However, not all patients and their treating physicians are adequately informed on this regard. In the Mexican survey, only 31% of young breast cancer patients recalled having received information from their providers regarding possible infertility following cancer therapy<sup>7</sup>. As shown in another recent survey conducted among physicians participating at the 3<sup>rd</sup> ESO-ESMO Breast Cancer in Young Women Conference (BCY3), 36% of the responders have never consulted the available international guidelines on fertility preservation in cancer patients<sup>12</sup>. Hence, further educational initiatives and

distribution of information are needed to improve knowledge around this topic and adherence to available guidelines.

The aim of the present review is to focus on the risk of anticancer treatment-related infertility and POF in young breast cancer patients, to summarize the current knowledge on the available options for fertility preservation, and to discuss the safety issues of pregnancy in breast cancer survivors. Furthermore, this review aims to highlight the specific clinical challenges in this field faced by physicians and patients from Latin American countries.

## IMPACT OF BREAST CANCER ON FUTURE PREGNANCIES AND FERTILITY POTENTIAL

Despite the fact that approximately half of the young women with newly diagnosed early-stage breast cancer desire to have a pregnancy<sup>13</sup>, less than 10% manage to subsequently become pregnant<sup>14</sup>. It is well known that female cancer survivors have significantly lower pregnancy rates as compared to the general population of a similar age hazard ratio [HR]: 0.61; 95% confidence intervals [CI]: 0.58-0.64<sup>15</sup>. Furthermore, among cancer survivors, young women with breast cancer have the lowest pregnancy rate, with a 67% reduced chance of future pregnancies as compared to the general population (HR: 0.33; 95% CI: 0.27-0.39)<sup>15</sup>. There are two possible main explanations for these findings: the concerns of providers and patients of a possible negative impact of pregnancy on the recurrence of breast cancer, and the gonadotoxic impact of the anticancer therapies required to treat this type of disease.

Recent surveys have confirmed the skepticism of some physicians on the safety of pregnancy in breast cancer survivors. A recent Italian survey showed that 46% of the surveyed oncologists believed that pregnancy affects the prognosis of young women with breast cancer, and 49% supported the statement that an increase in estrogen levels during pregnancy might stimulate the growth of hidden cancer cells<sup>16</sup>. Similarly, 30% of the physicians responding to the BCY3 survey agreed or were neutral on the statement that pregnancy in breast cancer survivors may increase the risk of recurrence<sup>12</sup>.

Similar findings have been recently reported in Mexico, with only 25% of surveyed healthcare providers considering pregnancy after breast cancer safe (unpublished data). However, current data support the safety of pregnancy after breast cancer diagnosis. It has been shown that a pregnancy in breast cancer survivors does not have a negative prognostic impact, regardless of the hormone receptor status of the tumor. In the meta-analysis by Azim, et al., including 14 retrospective control-matched studies with 1,244 cases and 18,145 controls, breast cancer survivors with a pregnancy during follow-up showed a 41% reduced risk of death compared to patients who did not become pregnant (pooled relative risk [PRR]: 0.59; 95% CI: 0.50-0.70)<sup>17</sup>. When correcting for the “healthy mother effect”, a 15% non-significant reduction in the risk of death for women who subsequently became pregnant was also observed (PRR: 0.85; 95% CI: 0.53-1.35)<sup>17</sup>. A subsequent large multicenter retrospective cohort study adjusting for the “healthy mother effect” confirmed the safety of pregnancy in breast cancer survivors and even specifically in those with endocrine-sensitive disease<sup>18</sup>. In this study, 333 pregnant patients and 874 matched non-pregnant patients were included. No difference in disease-free survival (DFS) was observed between pregnant and non-pregnant patients both in the estrogen receptor-positive cohort (HR: 0.91; 95% CI: 0.67-1.24;  $p = 0.55$ ) and in the estrogen receptor-negative group (HR: 0.75; 95% CI: 0.51-1.08;  $p = 0.12$ ). Patients in the pregnant cohort had a better overall survival (OS) than the non-pregnant group (HR: 0.72; 95% CI: 0.54-0.97;  $p = 0.03$ ); no interaction according to estrogen receptor status was observed ( $p = 0.11$ )<sup>18</sup>. A more recent meta-analysis including 19 studies with 1,829 cases and 21,907 controls confirmed the lack of negative prognostic impact of pregnancy following breast cancer<sup>19</sup>. On the contrary, pregnant patients showed a significantly reduced risk of death compared to non-pregnant patients (HR: 0.63; 95% CI: 0.51-0.79). A subgroup analysis accounting for the “healthy mother effect” reported similar results (HR: 0.65; 95% CI: 0.52-0.81)<sup>19</sup>. Hence, taking into account all these findings, after adequate treatment and follow-up, pregnancy in breast cancer survivors, including in those with hormone receptor-positive disease, should not be discouraged anymore<sup>20</sup>.

A second important explanation for the low pregnancy rate in breast cancer survivors is the negative

impact of anticancer treatments on patients’ gonadal function. The key factors associated with treatment-related POF risk in breast cancer patients include administration of chemotherapy and use of endocrine therapy<sup>5</sup>, and, even more importantly, age of the patient and anti-Müllerian hormone (AMH) level at the time of diagnosis<sup>21,22</sup>. The major limitation in counseling young patients on the likelihood of developing treatment-related POF is the fact that menstrual function assessed at different time-points after the end of chemotherapy was considered a surrogate indicator of gonadal activity<sup>23</sup>. In fact, it is known that resumption of menstruation is not always associated with recovered ovarian function, and women previously exposed to chemotherapy with cyclic menstrual activity may still have diminished ovarian reserve and reduced fertility potential<sup>24</sup>. Taking into account this limitation during oncofertility counseling, all young women with breast cancer should be advised that a higher risk of developing treatment-related POF is associated with older age (closer to the natural age of menopause) at the time of treatment, the use of alkylating agents (particularly cyclophosphamide), and the need for prolonged adjuvant endocrine therapy<sup>5</sup>. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 trial comparing three different adjuvant chemotherapy regimens (sequential doxorubicin [A] and cyclophosphamide [C] followed by docetaxel [T; AC→T], AT, and TAC), amenorrhea rates by treatment arm were assessed with standardized questionnaires at baseline and at follow-up visits every six months<sup>25</sup>. A different percentage of patients experienced at least 24 months of amenorrhea according to their age at the time of treatment, ranging from 61% in women under the age of 40 to 100% in patients older than 50 years. Amenorrhea rates at 12 months after the start of therapy were significantly different between treatment arms: 37.9% for AT, 57.7% for TAC, and 69.8% for AC→T ( $p < 0.001$ ). The addition of tamoxifen increased the risk of treatment-related amenorrhea; patients who received AT chemotherapy without tamoxifen showed the lowest rate of amenorrhea (20-25% across the two-year period of observation)<sup>25</sup>. Recent data have confirmed the intermediate risk of treatment-related POF with the use of anthracycline-based or anthracycline- and taxane-based regimens (ranging from 43 to 57%) with both standard administration and dose-dense schedules<sup>26</sup>. These data

further highlight the need to counsel all young patients at risk of treatment-related POF and infertility, and to refer those interested in fertility preserving procedures to fertility clinics as soon as possible before starting anticancer treatments<sup>8,9</sup>.

## AVAILABLE OPTIONS FOR FERTILITY PRESERVATION

In breast cancer patients, the available options for fertility preservation include temporary ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa) during chemotherapy, embryo/oocyte cryopreservation, and cryopreservation of ovarian tissue. Specific pro and contra and country availability are presented in table 1; these should be discussed and made clear during oncofertility counseling (Fig. 1).

Table 2 describes the more suitable candidates for the different fertility preserving procedures among young patients with breast cancer.

### Temporary ovarian suppression with GnRHa during chemotherapy

Temporary ovarian suppression with GnRHa during chemotherapy has been studied as a strategy to preserve gonadal function during the administration of cytotoxic therapy. Its major advantages are the wide availability, the lack of delay in the initiation of anticancer treatments, and no requirement for a surgical procedure. However, due to the previous conflicting results on its efficacy, the protective role of temporary ovarian suppression with GnRHa during chemotherapy has been largely debated over the past years<sup>27-30</sup>, and this strategy was considered experimental by the 2013 international guidelines on fertility preservation in cancer patients<sup>8,9</sup>. Nevertheless, several recent important updates on this topic have supported the protective role of this strategy in young women with breast cancer undergoing (neo)adjuvant chemotherapy<sup>31</sup>.

The two largest phase III trials investigating the protective role of temporary ovarian suppression with GnRHa during chemotherapy randomly assigned young breast cancer patients with early-stage disease to receive (neo)adjuvant chemotherapy plus

concurrent GnRHa or cytotoxic therapy alone<sup>32,33</sup>. All the 257 patients included in the POEMS-SWOG S0230 trial had hormone receptor-negative disease<sup>32</sup>, while 80% of the 281 women enrolled in the PROMISE-GIM6 study had hormone receptor-positive tumors<sup>34</sup>. Both studies showed consistent results in terms of the protective gonadal effect of this strategy; as compared to cytotoxic therapy alone, the concurrent administration of GnRHa and chemotherapy showed to significantly reduce the risk of developing treatment-induced POF, from 22 to 8% in the POEMS-SWOG S0230 trial odds ratio [OR]: 0.30; 95% CI: 0.09-0.97;  $p = 0.04$ )<sup>32</sup> and from 25.9 to 8.9% in the PROMISE-GIM6 study (OR: 0.28; 95% CI: 0.14-0.59;  $p < 0.001$ )<sup>34</sup>. More patients treated with GnRHa during chemotherapy than those receiving cytotoxic therapy alone had a subsequent pregnancy; however, the result was significant in the POEMS-SWOG S0230 trial (22 vs. 12 women; OR: 2.45; 95% CI: 1.09-5.51;  $p = 0.03$ )<sup>32</sup> and not in the PROMISE-GIM6 study (8 vs. 3 women; age-adjusted HR: 2.40; 95% CI: 0.62-9.22;  $p = 0.20$ )<sup>33</sup>.

When the results of all the 12 randomized studies assessing the role of temporary ovarian suppression with GnRHa during chemotherapy were pooled together, a significant reduction in the risk of developing treatment-induced POF was observed with the use of this strategy (OR: 0.36; 95% CI: 0.23-0.57;  $p < 0.001$ )<sup>35</sup>. Moreover, although the numbers remain low, with only five studies reporting this outcome, the meta-analysis showed a significantly higher number of patients with a subsequent pregnancy (33 vs. 19 women) when adding GnRHa to chemotherapy (OR: 1.83; 95% CI: 1.02-3.28;  $p = 0.041$ ). Despite only three studies having reported data on the potential safety of administering GnRHa concurrently with chemotherapy, no apparent negative impact on DFS was observed (HR: 1.00; 95% CI: 0.49-2.04;  $p = 0.939$ )<sup>35</sup>.

Taking into account these findings, recent guidelines have acknowledged the clinical utility of temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients interested in preserving ovarian function and/or fertility<sup>4,36</sup>. The cost of the procedure for six months of treatment during (neo)adjuvant chemotherapy is approximately 1,000 dollars for each patient. In Italy, the Italian Ministry of Health has recently granted coverage for this strategy to all young breast cancer patients<sup>36</sup>. Due to the

Table 1. Main characteristics of the different strategies for fertility preservation

| Type of strategy   | Main results  | Pro  | Contra   |
|--|---|--|--|
| Temporary ovarian suppression with GnRHa during chemotherapy | <ul style="list-style-type: none"> <li>– Reduction in the risk of developing treatment-induced POF (OR; 0.36; 95% CI: 0.23-0.57; p &lt; 0.001)</li> <li>– Higher number of patients with a subsequent pregnancy (33 vs. 19 women; OR: 1.83; 95% CI: 1.02-3.28; p = 0.041)</li> <li>– No apparent negative impact on survival (HR: 1.00; 95% CI: 0.49-2.04; p = 0.939)</li> </ul>  | <ul style="list-style-type: none"> <li>– No need for controlled ovarian hyperstimulation</li> <li>– No delay in the initiation of anticancer therapies</li> <li>– No surgery required</li> <li>– Widely available</li> <li>– Limited cost</li> </ul> | <ul style="list-style-type: none"> <li>– No data on long-term preservation of ovarian function (age at menopause)</li> <li>– Limited data on fertility preservation potential</li> <li>– Limited data on long-term survival outcomes</li> </ul>  |
| Embryo/oocyte cryopreservation                               | <ul style="list-style-type: none"> <li>– Variable live birth rates according to age at the time of the procedure (data from the infertile non-oncologic population): 22.7% for patients &lt; 34 years, 18.1% for women aged 35-39, and &lt; 10% for women &gt; 40 years</li> <li>– Pregnancy rate of 51.5% in a series of 33 breast cancer patients</li> <li>– No apparent negative impact on survival in breast cancer patients (HR: 0.77; 95% CI: 0.28-2.13; p = 0.61)</li> </ul> | <ul style="list-style-type: none"> <li>– Most reliable results on fertility preservation potential (in infertile non-oncologic women)</li> <li>– Minor surgery required</li> <li>– Good availability</li> </ul>                                      | <ul style="list-style-type: none"> <li>– No preservation of ovarian function</li> <li>– Need for controlled ovarian hyperstimulation</li> <li>– Possible delay in the initiation of anticancer therapies</li> <li>– Limited efficacy and safety data in cancer patients</li> <li>– Need for a specialized fertility preservation facility</li> <li>– High cost*</li> </ul> |
| Cryopreservation of ovarian tissue                           | <ul style="list-style-type: none"> <li>– Successful recovery of ovarian function expected within 3-6 months</li> <li>– Possible sustained longevity of ovarian function</li> <li>– Almost 100 babies born worldwide</li> <li>– Live birth rate estimated around 30%</li> </ul>  | <ul style="list-style-type: none"> <li>– No need for controlled ovarian hyperstimulation</li> <li>– Minimal or no delay in the initiation of anticancer therapies</li> <li>– Preservation of both fertility and ovarian function</li> </ul>          | <ul style="list-style-type: none"> <li>– Need for 2 surgical procedures</li> <li>– Limited efficacy and safety data in cancer patients</li> <li>– Need for a specialized fertility preservation facility</li> <li>– Risk of reintroduction of malignant cells at the time of transplantation</li> </ul>  |

\*May vary by country.

CI: confidence intervals; GnRHa: gonadotropin-releasing hormone agonists; HR: hazard ratio; OR: odds ratio; POF: premature ovarian failure.

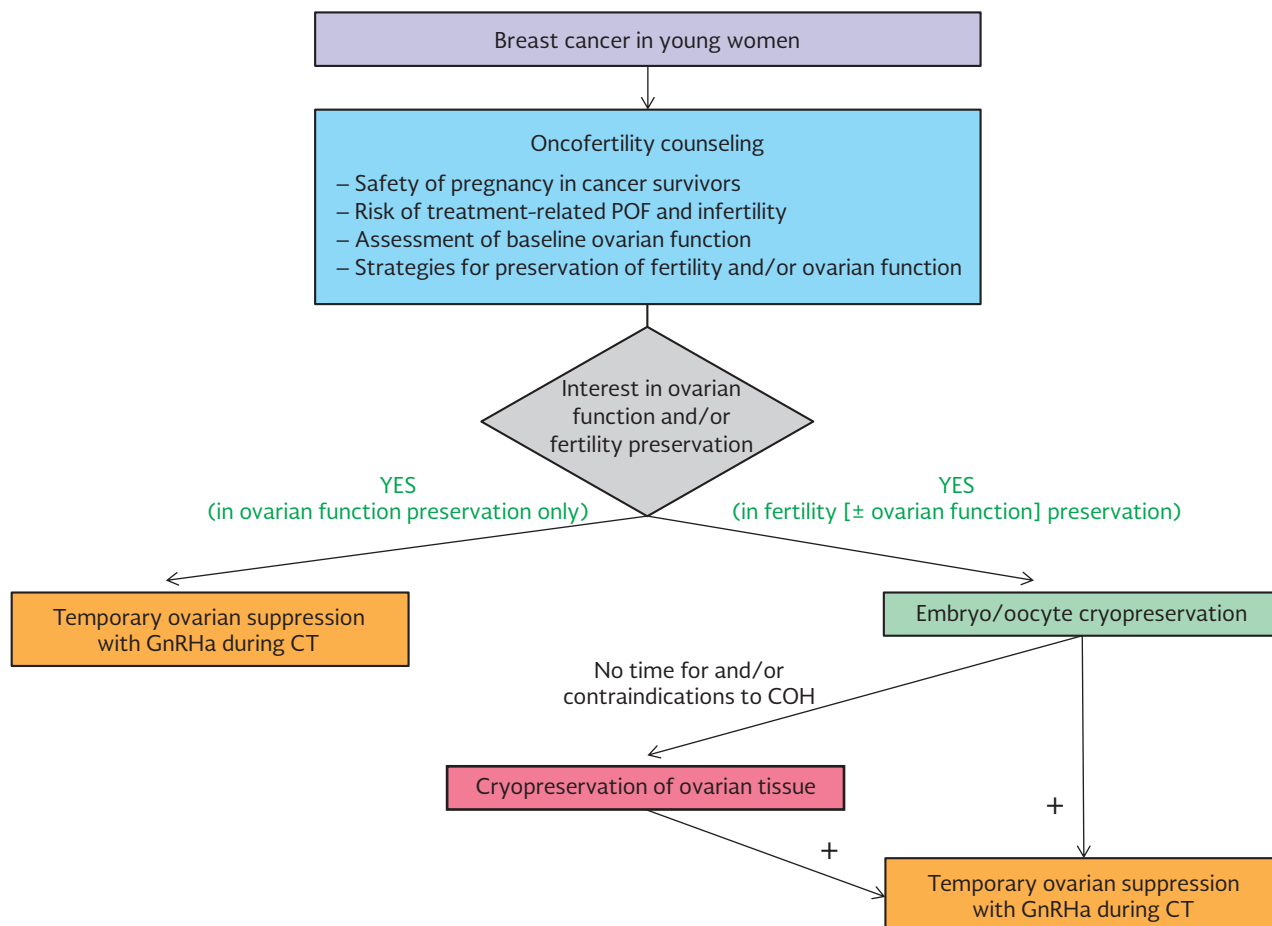
lower cost as compared to cryopreservation procedures, temporary ovarian suppression with GnRHa during chemotherapy may also become an option in Latin America. However, this should not be regarded as an alternative of care, and embryo/oocyte cryopreservation should be always considered as the first strategy to be discussed with patients willing to preserve fertility (Fig. 1). Final results from the MOMMY study, an ongoing individual patient data meta-analysis investigating the role of temporary ovarian suppression with GnRHa during chemotherapy in breast cancer patients (PROSPERO registration number: CRD42014015638)<sup>20</sup>, are awaited to provide final

evidence regarding the efficacy and safety of this procedure.

### Embryo/oocyte cryopreservation

Embryo/oocyte cryopreservation are standard strategies for fertility preservation in female cancer patients<sup>8,9</sup>. They require controlled ovarian hyperstimulation (COH), which induces supra-physiological estradiol levels along with the development of several follicles<sup>37</sup>. In infertile women without cancer, embryo cryopreservation following COH demonstrated the most reliable results in terms of subsequent

Figure 1. Oncofertility counseling and indications for the different strategies for fertility preservation in young breast cancer patients. COH: controlled ovarian hyperstimulation; CT: chemotherapy; GnRH $\alpha$ : gonadotropin-releasing hormone agonists; POF: premature ovarian failure.



pregnancies. The success of embryo cryopreservation is strongly dependent on the patient's age at the time of oocyte retrieval and fertilization<sup>37</sup>. Using this procedure, the live birth rates according to the 2012 European Society of Human Reproduction and Embryology (ESHRE) were 22.7% for patients younger than 34 years, 18.1% for women aged 35-39, and less than 10% for women older than 40 years<sup>38</sup>. In experienced centers, similar results can be obtained after oocyte cryopreservation<sup>39,40</sup>.

In breast cancer patients, COH protocols have been adjusted in order to avoid the possible detrimental impact of high estradiol levels on cancer cell proliferation using concomitant administration of letrozole (an aromatase inhibitor)<sup>41,42</sup> or tamoxifen (an estrogen receptor modulator)<sup>43-45</sup>.

### **Letrozole-associated controlled ovarian hyperstimulation**

In the protocol developed by Oktay, et al., letrozole-associated COH cycles were initiated either in a "standard" or "random-start" protocol according to the patient's menstrual cycle phase and the urgency to start chemotherapy<sup>41,42</sup>. In the "standard" protocol, letrozole was initiated on the second or third day of menstruation, followed two days later by gonadotropin administration. A GnRH $\alpha$  was administered as soon as one follicle reached 14 mm or estradiol levels rose to 250 pg/ml, to avoid premature luteinization. In the "random start" protocol, letrozole, gonadotropins, and GnRH $\alpha$  were initiated at the same time throughout COH until ovulation triggering<sup>37</sup>.

Table 2. The best candidates for the different strategies for fertility preservation among young patients with breast cancer

| Type of strategy   | Best candidates  |
|--|--|
| Temporary ovarian suppression with GnRHa during chemotherapy | <ul style="list-style-type: none"> <li>– Patients interested in ovarian function preservation only (no interest in fertility preservation)</li> <li>– Patients interested in fertility preservation (age &lt; 38 to 40 years) but<sup>*</sup>:<br/>Following embryo/oocyte cryopreservation, and/or<br/>No access to embryo/oocyte cryopreservation</li> </ul> |
| Embryo/oocyte cryopreservation                               | <ul style="list-style-type: none"> <li>– Patients interested in fertility preservation with:<br/>Age &lt; 38 to 40 years, and<br/>Good ovarian reserve, and<br/>The possibility to delay the start of chemotherapy (≥ 2 weeks)<sup>†</sup></li> </ul>  |
| Cryopreservation of ovarian tissue                           | <ul style="list-style-type: none"> <li>– Patients aged &lt; 36 years interested in fertility preservation with high risk of premature ovarian insufficiency:<br/>Who cannot delay treatment initiation, and/or<br/>With contraindication to controlled ovarian hyperstimulation</li> </ul>   |

<sup>\*</sup>The use of temporary ovarian suppression with GnRHa during chemotherapy is not an alternative to embryo/oocyte cryopreservation.

<sup>†</sup>Despite the use of random-start protocols for controlled ovarian stimulation, 2 weeks are usually required.

GnRHa: gonadotropin-releasing hormone agonists.

Ovulation triggering was commonly induced by human chorionic gonadotropin or GnRHa in case of ovarian hyperstimulation syndrome risk<sup>37</sup>. When estradiol levels remained high after oocyte retrieval, letrozole was administered again until it declined to < 50 pg/ml. Recently, Goldrat, et al. have shown high progesterone levels during early luteal phase following this protocol<sup>46</sup>. As progesterone may be as important as estradiol on tumorigenesis<sup>47</sup>, the authors recommended triggering ovulation with GnRHa in all breast cancer patients, regardless of ovarian hyperstimulation syndrome risk, and avoiding administration of letrozole after oocyte retrieval<sup>46</sup>.

Conflicting results have been reported regarding the number of mature oocytes yielded in letrozole-associated COH compared to patients undergoing COH without letrozole<sup>48,49</sup>. Nonetheless, in 2015, Oktay, et al. reported the success rate of oocytes/embryos cryopreservation using letrozole-associated COH in the largest breast cancer cohort reported to date<sup>45</sup>. Thirty-three breast cancer survivors who had undergone embryo cryopreservation with letrozole-associated COH returned for 40 frozen embryo transfers (either to herself or a gestational carrier), which resulted in 18 deliveries of 25 healthy babies. The live-birth rate (18/40, 45%) was similar to the general infertile population<sup>45</sup>. Furthermore, the same group has shown reassuring results regarding the safety of performing COH<sup>50</sup>. They compared the relapse rate in a cohort of 119 breast cancer patients who underwent letrozole-associated COH for fertility preservation with 152 matched patients who did not undergo

fertility preserving procedures. All characteristics were comparable between groups except for lower lymph node involvement in the group undergoing embryo cryopreservation (34 vs. 48%;  $p = 0.02$ ). After a mean follow-up of more than five years, no survival difference was observed, with a relapse rate of 5.0 and 5.5% in patients who underwent or not COH, respectively ( $p = 0.86$ ), with a HR for recurrence after embryo cryopreservation of 0.56 (95% CI: 0.17-1.9;  $p = 0.36$ )<sup>50</sup>.

### **Tamoxifen-associated ovarian hyperstimulation**

Tamoxifen represents an alternative to letrozole in COH for embryo/oocyte cryopreservation in breast cancer patients<sup>37</sup>. It is usually combined with gonadotropins at doses ranging from 20 to 60 mg/day until the day of ovulation trigger<sup>44,51</sup>. The number of mature oocytes and embryos obtained with tamoxifen-associated COH were similar to results achieved after COH without tamoxifen in endocrine receptor-negative breast cancer patients ( $12.65 \pm 8.04$  vs.  $10.22 \pm 6.08$ ;  $p = 0.183$ , and  $8.51 \pm 6.57$  vs.  $6.41 \pm 4.64$ ;  $p = 0.265$ , respectively)<sup>44</sup>. However, there are some safety issues related to the use of tamoxifen-associated COH, mainly due to the delay in achieving steady state for tamoxifen and its bioactive metabolite endoxifen (approximately two months)<sup>52</sup>. After daily administration of 60 mg of tamoxifen in four patients who underwent fertility preservation COH, Balkenende, et al. showed a great variability in the serum levels of the drug and its

metabolite, achieving insufficient concentration in one of the patients<sup>52</sup>.

### ***In vitro* maturation**

In some cases, COH is not a feasible option for fertility preservation, mainly due to time constraints as well as oncologists' and/or patients' safety concerns on the risk of breast cancer recurrence. Immature oocytes collected at any phase of the menstrual cycle followed by *in vitro* maturation (IVM) may hence be a viable option. Maturation and fertilization rates with this technique vary between 50-70% and 70-80%, respectively<sup>53,54</sup>. However, implantation, clinical pregnancy, and live birth rates as well as miscarriage rates have been described mainly for non-oncologic patients with polycystic ovary syndrome. A recent study comparing the pregnancy outcomes after IVM procedure or standard *in vitro* fertilization showed that IVM was less efficient after fresh embryo transfer (live birth rates of 18 vs. 31%;  $p = 0.021$ )<sup>55</sup>. However, frozen-thawed embryo transfers showed similar results between groups, suggesting that IVM might be an interesting alternative option for fertility preservation in breast cancer patients<sup>55</sup>.

### **Cryopreservation of ovarian tissue**

In this technique, ovarian tissue from either ovarian biopsies or the whole ovary is collected by laparoscopy, and small fragments are cryopreserved for a possible future auto-transplantation to restore ovarian function and fertility. Immature oocytes can also be collected *ex vivo* on the ovarian tissue and cryopreserved after IVM during the procedure when performed before gonadotoxic treatments. The main advantages of this procedure are avoidance of delay in chemotherapy initiation and hormone exposure associated to COH.

The technique is still considered as experimental, but almost 100 babies were born worldwide after ovarian tissue transplantation at an orthotopic site, and live birth rates have been estimated around 30%<sup>56,57</sup>. Van Der Ven, et al. have recently reported pregnancies of 16 grafted patients<sup>56</sup>. Among them, five were breast cancer survivors aged between 28-38 years at the time of ovarian tissue cryopreservation. All these patients became pregnant and delivered following ovarian tissue transplantation<sup>56</sup>. Nevertheless, it should be kept in mind that the success rate depends mainly on

the age and ovarian reserve (hence follicular density) at the time of tissue cryopreservation. Young patients diagnosed with breast cancer are often already in their 30s and might subsequently have a lower chance of pregnancy following ovarian tissue grafting<sup>58</sup>.

Some safety issues are still under investigation, especially regarding the possibility of reintroducing malignant cells during a transplantation procedure<sup>20</sup>. Luyckx, et al. analyzed 13 thawed ovarian tissues from advanced breast cancer patients using histology, immunohistochemistry, xenografting to mice, and quantitative polymerase chain reaction for gene expression of mammaglobin 2 (MGB2)<sup>59</sup>. They found no microscopic cancer cells and xenograft results were also reassuring; however, MGB2 expression was positive in four out of 13 cases<sup>59</sup>. Other studies assessed the usefulness of molecular markers for the detection of residual disease in the ovarian tissue of breast cancer patients. Using PCR technique, mammaglobin 1 (MGB1), gross cystic disease fluid protein 15, and small breast epithelial mucin showed the highest predictive values in the detection of micro-metastases in ovarian tissue of breast cancer<sup>60-63</sup>. Hoekman, et al. detected positive MGB1 expression in ovarian tissue in one out of three patients with breast cancer and sentinel lymph node involvement<sup>61</sup>. Results are reassuring overall, but further studies are needed to confirm the clinical relevance of the detection of these markers to adequately counsel patients.

## **ACCESS TO FERTILITY PRESERVATION STRATEGIES IN LATIN AMERICA**

Although oncofertility counseling should now be considered an essential component in the management of young women with breast cancer, in Latin America efforts are predominantly dedicated to improve cancer survival rates. Hence, fertility preservation issues are often neglected. Only a minority of patients receives information about treatment-related POF and infertility by their physicians, and a limited number of them are ultimately referred to a fertility specialist<sup>7,64</sup>. Some of the particular challenges that can explain the lack of routine practice of fertility preservation procedures in Latin America include inequitable distribution of cancer centers and specialists, lack of public healthcare coverage for supportive care, and significant socioeconomic gaps.



The availability of specialized fertility preservation centers in Latin America is limited, and these units are usually concentrated in major cities and located in tertiary care facilities. The latest edition of the Latin American Registry for Assisted Reproductive Technologies reported that only 158 assisted reproduction facilities are available in Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, Peru, Dominican Republic, Uruguay, and Venezuela<sup>65</sup>. This number is far behind the available centers in more developed countries such as the USA, where over 440 clinics provide service to patients seeking to overcome infertility<sup>66</sup>. Hence, fertility units are out of reach for a large proportion of patients in Latin America.

The low access to fertility preserving procedures in Latin America is also explained by the fact that these options are not covered either by the governments or by private health insurers<sup>64</sup>. This represents a direct and often unreachable out of pocket expense for patients, particularly in limited resource settings with income inequities. As an example, in a web-based survey conducted in Mexico among 241 oncology health-care providers, the most prevailing factor that hindered the referral of cancer patients to fertility preservation was its high cost (unpublished data). In the previously mentioned survey in Mexican patients regarding their fertility concerns in two referral centers in Mexico with access to public health services, only 3% of patients considered themselves able to afford extra expenses beyond oncologic treatment<sup>7</sup>. As a consequence, in such countries where fertility preservation depends on the individual capacity to afford its coverage, the access to these procedures will likely remain low.

Another important reason explaining the low referral rates of cancer patients to fertility clinics in Latin America is the physician's inconsistent disclosure of infertility risks. There are several possible explanations for these findings: the high proportion of advanced breast cancer cases in young patients, the concern of physicians of delaying cancer treatment if fertility preservation is pursued, the lack of knowledge on the effects of systemic therapy on fertility, and the concern about the effect of pregnancy on breast cancer prognosis. In the aforementioned Mexican survey, for example, a shocking 75% of healthcare providers considered pregnancy unsafe after breast cancer diagnosis (unpublished data).

## FUTURE PERSPECTIVES

Thanks to the improved survival outcomes observed in recent years, a growing attention has been given to the quality of life issues faced by young women with breast cancer such as fertility preservation and concerns related to future pregnancies. However, several challenges remain for young women with breast cancer considering undergoing fertility preserving procedures. Further, specific issues should be considered on this regard for Latin American patients and physicians. Hence, additional efforts are needed in the coming years to overcome these deficiencies and improve the correct referral of breast cancer patients to fertility preservation strategies.

First, it is crucial to improve the equality in access to different strategies for fertility preservation for patients from all countries. The implementation of a federal policy recognizing the right to start a family as a human right can provide universal access to assisted reproductive technologies. This is the case of Argentina, where the number of assisted reproductive cycles per population has increased in the general population since the approval in 2013 of the law number 26.862 ("Acceso integral a los procedimientos y técnicas médico-asistenciales de reproducción medicamente asistida"). Furthermore, the promotion of local alliances between oncology and reproductive centers could potentially increase cross-specialty communication and referrals, as well as diminish costs. Likewise, the integration of dedicated programs for young breast cancer patients has also changed the current breast cancer treatment paradigm to not only treat and cure the disease, but to also give weight to the quality of life of young survivors. As an example, the implementation of the "PYNK" initiative in Canada<sup>67</sup> and the "Joven y Fuerte" program in Mexico<sup>68</sup> has indeed increased the number of timely referrals to fertility preservation procedures.

Second, despite increasing awareness about the different strategies for fertility preservation, there is lack of data on patient preferences and needs towards the different strategies for fertility preservation<sup>69</sup>. Data from the western world suggest that despite the great proportion of women concerned about fertility at the time of diagnosis, a limited percentage of patients (approximately 10%) decided to take special steps to lessen their risk of infertility with the use of fertility preserving procedures<sup>6</sup>. In the Mexican study, less than 1% pursued fertility preserving

procedures; different reasons might explain this low proportion such as limited access due to high costs and unawareness of the infertility risks associated with oncologic treatment<sup>7</sup>. Prospective efforts, such as the Italian PREFER study (ClinicalTrials.gov Identifier: NCT02895165), the HOHO study in the USA<sup>6</sup>, the PYNK program in Canada<sup>67</sup>, and the Mexican Joven y Fuerte Program<sup>68</sup>, among others, are currently ongoing to try to better understand the preferences and needs of patients towards the different strategies. This information is crucial to improve the quality of oncofertility counseling, but also from a public health perspective for better allocation of resources.

Third, further research efforts are needed to generate more solid data to counsel *BRCA*-mutated women on the safety of pregnancy after breast cancer, the impact of anticancer treatments on their ovarian function, and the feasibility of the different strategies for fertility preservation<sup>70</sup>. This is also important to be taken into account in women from Latin American countries where the prevalence of *BRCA* mutations (ranging from 1.2 to 4.9%) is very similar to that of the non-Hispanic population in the USA<sup>71</sup>. Specific issues should be considered in the field of fertility preservation in cancer patients for *BRCA* carriers. In fact, it has been hypothesized that mutations in the *BRCA* genes may be associated with primary occult ovarian insufficiency that might potentially lead to subsequently lower reproductive potential, increased risk of treatment-related gonadotoxicity, and low response to fertility treatments<sup>72</sup>. However, very limited clinical data exist in this regard in *BRCA*-mutated breast cancer patients, and further research in this field should be considered a priority.

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