

## Ovarian Reserve and Breast Cancer

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### Abstract

**Background:** Historically, oncological management focused on the cure of cancer, regardless of the long-term consequences; the advances in detection and treatment improve the results that impose several considerations on the quality of life and preservation of fertility.

**Objective:** To determine the gonadal damage of patients with breast cancer. *Material and method.* A prospective and comparative observational study of 14 patients with a history of breast cancer who received chemotherapy (group 1), chemotherapy and radiotherapy (group 2), independently of surgical treatment and 4 patients without cancer, control group (group 3), was performed. Hormone Follicle Hormone was taken, antral follicular count and ovarian volume with color Doppler ultrasound.

**Results:** The 14 patients in different clinical stages of breast cancer, we find that Chemotherapy and Radiotherapy decrease the follicular count, mainly when both are administered; with significant damage between groups 1 and 2; the follicle stimulating hormone levels increased in groups 1 and 2 with respect to the control group, without differences in the tests and the different chemotherapy schemes, all cause ovarian damage and present ovarian dysfunction. Currently there are different techniques to determine the ovarian reserve, the best is the measurement of antimülleriana hormone.

**Conclusion:** It is important to implement individual preventive measures that improve the quality of life including reproduction; due to the risk of ovarian failure due to oncological management, which increases the risk of chronic-degenerative diseases, increasing morbidity and mortality, and the cost of health.

**Keywords:** breast cancer, preservation of fertility, oncological management, chemotherapy, radiotherapy, ovarian reserve tests.

### BACKGROUND

Breast cancer is a global public health problem and in the last 25 years the number of new cases has doubled annually; it is common in women of reproductive age; 6% are diagnosed before 40 years of age 1,2; 25% in women of reproductive age and is an important cause of cancer death; early diagnosis and effective oncological management increases the survival of patients mainly in developed countries and the preservation of fertility is an important part of their quality of life 3-5.

The evaluation of function and ovarian reserve, to preserve fertility, are important in these women of reproductive age with breast cancer under

cancer treatment 6,7. Chemotherapy (Qt) can cause premature ovarian failure and infertility, the age of the patient, type and dose of chemotherapy are the main factors that determine the extent of ovarian damage. The accelerated and premature depletion of germ cells caused by direct damage to the primordial follicle is the main mechanism of gonadal insufficiency; in addition, of the ovarian and vascular stromal damage. Ovarian reserve tests help predict the reproductive future to individualize fertility preservation strategies before chemotherapy. The level of the antimülleriana hormone or Antimüllerian hormone (AMH) represents the most useful marker of the ovarian reserve, the account of antral follicles or antral follicle count; (AFC) reliable non-invasive method that is measured

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by transvaginal ultrasonography in the early follicular phase together with follicle-stimulating hormone (FSH) are tests used to determine the ovarian reserve; basal levels of estradiol can provide useful additional information, especially when FSH levels are within the normal range 8,9.

Historically, oncological management focused on the cure of breast cancer; Regardless of the long-term consequences, it is the most commonly diagnosed cancer in women, accounting for 26% of all cancers in women 10; in premenopausal women, the incidence increased from 8 to 9% per year, 11,12 with an increase in the incidence in patients under 30 years of age, constituting 1-2%; the age range of 35 to 40 years of age refers to women of reproductive age with differences in risk factors, tumor characteristics, clinical presentation and considerations on fertility, self-image, quality of life, personal goals, etc; reproductive age is an independent risk factor for recurrence and death; the survival rate in women under 30 years of age at 5 to 10 years is 48% and 36% and in those over 30 years of age 59 and 37% respectively 13,14.

The development of amenorrhea secondary to Qt is related to the age of the women, type and total dose; 80 to 95% of developing amenorrhea, in less than 40 years compared to 30 to 40% in people over 40 years of age and in those under 30 years, premature ovarian failure is uncommon; amenorrhea can be

reversible, some recover menstrual function months and occasionally years after Qt 15.

The preservation of fertility is an integral component of oncological management; approaches include cryopreservation of embryos or oocytes, ovarian transposition, conservative surgery, conservative medical treatment to delay radical surgery, and measures to avoid damaging the gonads, alone or in combination; now allows reproduction 15. The delay of motherhood increases the possibility of presenting cancer 16; It is reported that 1 in 250 women of reproductive age had cancer in childhood, 2% of children under 40 years developed cancer, half received oncological management that affected reproduction 8 due to gonadal damage 8,9 induced by Qt and Radiotherapy (Rt) ) 1,2,16-17, measures to preserve fertility 1,3,5 and preventive measures with multidisciplinary management; It is reported that women under 40 years of age with breast cancer, only 26% were discussed about fertility, but of these 90% requested to preserve fertility; the information is made during the diagnosis; some interventions to preserve fertility take time and could delay their oncological management; currently the Qt schemes cause less gonadal damage 1,3,5,18.19. The preservation of fertility requires individualization, with less gonadal damage, which depends on the type of oncological management, time available to initiate it, age of the patient, type of cancer, if the patient has a partner, costs and long-term problems (use of cryopreservation of gametes or embryos), table 1 11,12,13,15-19

**Table 1**

### Infertility risk related to cancer management in women

#### High risk

(> 80% risk of permanent amenorrhea) - External beam radiation to a field that includes the ovaries  
- CMF, CEF, CAF, TAC x 6 cycles in women ≥ 40 years

#### Intermediate risk

(40 - 60% risk of permanent amenorrhea) - CMF, CEF, CAF, TAC x cycles in women aged 30-39 years  
- AC x 4 cycles in women ≥ 40 years  
- AC or EC x 4 → Taxanos

#### Low risk

(<20% risk of permanent amenorrhea) - CMF, CEF, CAF, TAC x 6 cycles in women ≤ 30 years  
- AC x 4 cycles in women ≤ 40 years

#### Very low or no risk

(risk of permanent amenorrhea) - women <32 years old  
- Methotrexate -Fluorouracil -Vincristine  
- Tamoxifene

#### Unknown risk

(risk of permanent amenorrhea) - Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab), Tyrosine kinase inhibitors (erlotinib, imatinib)

CMF cyclophosphamide, methotrexate, fluorouracil; CEF cyclophosphamide, epirubicin, fluorouracil

CAF cyclophosphamide, doxorubicin, fluorouracil; TAC docetaxel, doxorubicin, cyclophosphamide

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The decrease in the number of germ cells causes infertility, the older age, mainly older than 35 years, the natural fertility of women decreases; the clinical evaluation of the ovarian reserve of the woman implies not only the age but also the increased levels of FSH, estradiol and inhibin B of ovarian origin and

by transvaginal ultrasound the antral count of ovarian follicles that decrease with age 9,18,20, ideally, a total of 12 or more follicles of both ovaries is adequate; the strategies to determine the ovarian reserve in current clinical practice, table 2.

### Table 2

#### Tests to identify the decreased ovarian reserve.

##### Serum follicle stimulating hormone level of the early follicular phase

FSH levels above 10 IU / l in the menstrual cycle of day 2 or 3 have a high specificity, but low sensitivity to predict low ovarian reserve.

##### Initial serum level of inhibin-B in follicular phase

Inhibin B levels are generally lower in women with decreased ovarian reserve. It is not considered a reliable measure of ovarian reserve due to the production of larger follicles and technique.

##### Serum level of AMH

The low threshold values of AMH have good sensitivity and specificity for low ovarian reserve. The technique may result in variation in the results

##### Ovarian volume

Low ovarian volume has a high specificity and low sensitivity to predict low ovarian reserve and has limited clinical utility as a marker of ovarian reserve

The antral follicular count (AFC)

The AFC low in the days of cycle 2-3 of the menstrual cycle has a high specificity to predict a low ovarian reserve. The accuracy depends on the operator

#### **AFC: antral follicles account; AMH: antimullerian hormone; FSH: follicle-stimulating hormone**

The term ovarian failure indicates the irreversible loss of ovarian function with failure of follicular development and ovulation, with hypoestrogenism. The loss of ovarian function in children under 40 years of age is considered premature ovarian failure. The impact of oncological management on ovarian function is hampered by the varied inconsistent definitions of amenorrhea and ovarian failure, and variable time of follow-up; in the majority they are 12 months to evaluate post-treatment amenorrhea, and up to 16 months in children under 40 years of age 11. The Qt and Rt lead to premature ovarian failure that depends on the age of the woman; there have been reports of pregnancies due to sporadic ovulation in women with ovarian failure 12.

treatment and 4 patients without a history of cancer, was performed. as a control group (group 3) in whom the FSH was taken on days 2 to 4 of the menstrual cycle, evaluation of the follicular count by transvaginal ultrasound on day 2 to 4 of the menstrual cycle in case of regular cycles, in case of amenorrhea, this was done without further specifications. Patients from 18 to 35 years of age were included in the 12-month remission period at the time of the study. Patients diagnosed with secondary amenorrhea due to any pathology were not included.

The indicators that were taken into account were the following: Age at diagnosis of Breast Cancer, number of pregnancies prior to treatment, clinical stage, oncological treatment received, duration of treatment, history of recurrence and post-treatment pregnancies.

We used Accuvix equipment with multi-frequency endocavitary transducer, color Doppler for transvaginal ultrasound, which was performed by

## MATERIAL AND METHOD

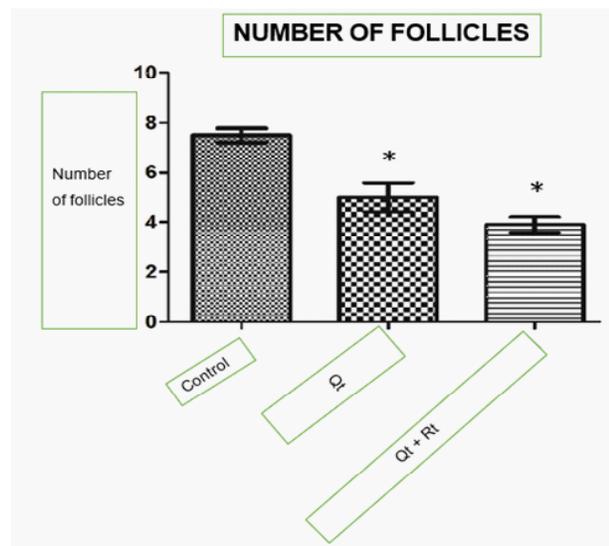
A prospective and comparative observational study of 14 patients from the Hospital Juárez de México with a history of breast cancer who received Qt (group 1), Qt and Rt (group 2), independently of the surgical

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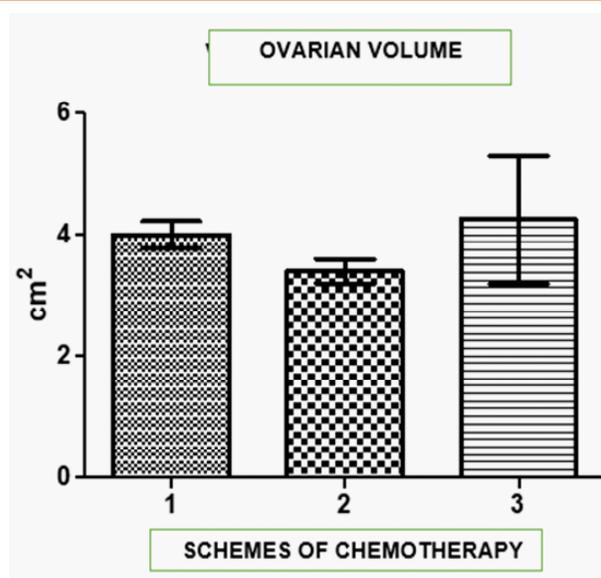
the same operator to reduce the range of operator-dependent error. The processing for the quantitative determination of FSH was carried out through the chemiluminescence immunoenzymatic analysis method in the central laboratory of the Hospital Juárez de México. The data was collected in the Graphpad prism 7.0 program.

### RESULTS

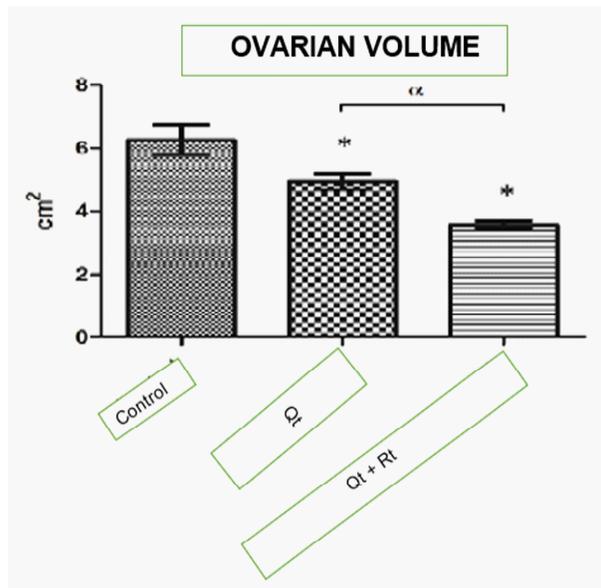
The 14 patients (100%) under oncological management, 11 patients (71.2%) developed amenorrhea and the remaining 3 patients (21.4%) presented irregular cycles, figure 9, although before the diagnosis all the patients reported having regular cycles; the treatment used was 4 for Qt in group 1 (relative frequency 28.57%), 10 with Qt and Rt in group 2 (relative frequency 10 with relative frequency 71.43%); for the clinical stages, the relative frequencies were 36% in clinical stage IIIA, 36% in clinical stage IIA, and 14% in clinical stage IIB, and 14% in stage IIIB. Three tests were carried out to evaluate the ovarian reserve: antral follicular count, ovarian volume, serum levels of FSH as a parameter of gonadal damage and the evaluation of the follicular count, the groups under oncological management and the control group were compared; finding significant differences in both cases, but not between them. The results indicate that both oncological treatments decrease the follicular count, mainly when both Qt and Rt are administered, figures 1-4.



**Fig. 1.** Antral follicular count. Each bar represents the mean  $\pm$  e.e (N = 18) Chemotherapy (Qt) (n = 4), Chemotherapy (Qt) and Radiotherapy (Rt) (n = 10), Control (n = 4). The \* indicate significant differences with respect to the control group, student t-test, unpaired ( $p < 0.05$ ).

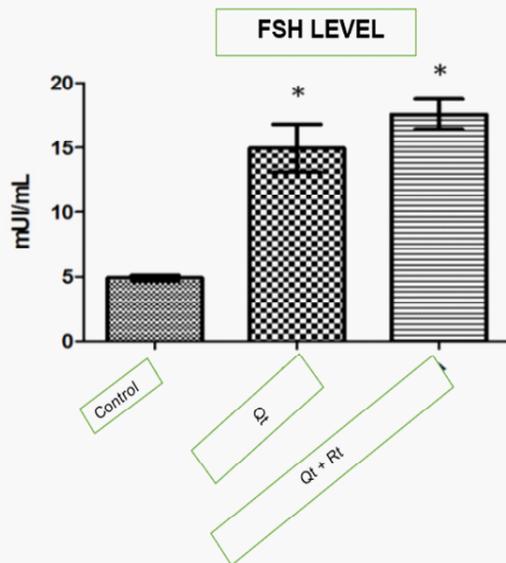


**Fig. 2.** Ovarian volume, each bar represents the mean  $\pm$  e.e. (N = 12). Group 1 (FAC Fluorouacil, Doxorubicin, Cyclophosphamide) (n = 8), Group 2 (Epirubicin, Cyclophosphamide) (n = 2), Group 3 (Doxorubicin, Cyclophosphamide) (n = 2), The \* indicate significant differences, test t of student, unpaired ( $p \leq 0.05$ ).



**Fig. 3.** Ovarian volume. Each bar represents the mean  $\pm$  e.e. (N = 18), Chemotherapy (n = 4), Chemotherapy and Radiotherapy (n = 10), Control (n = 4). The \* indicate significant differences with respect to the control group, student's t-test.

FSH levels increased significantly in groups 1 and 2 with respect to the control group, with greater gonadal damage in group 2 compared to group 1, figure 6.



**Fig. 4.** FSH level. Each bar represents the mean  $\pm$  e.e. ( $N = 18$ ), Chemotherapy ( $n = 4$ ), Chemotherapy and Radiotherapy ( $n = 10$ ), Control ( $n = 4$ ). The \* indicate significant differences with respect to the control group, student t-test, unpaired ( $p < 0.05$ ). The # indicate significant differences between treatments, student t test, unpaired ( $p < 0.05$ )

The patients who received the most common chemotherapy regimens were grouped into three groups: Fluorouracil, Doxorubicin, Cyclophosphamide (group 1), Epirubicin and Cyclophosphamide (group 2) and Doxorubicin and Cyclophosphamide (group 3) and only 12 patients were included (85.7 %) of the 14 previously established (100%). The two patients who did not group received Docetaxel, Carboplatin Anthracycline and Trastazumab (patient 1) and Cyclophosphamide, Paclitaxel, Cisplatin and Gemcitabine (patient 2) as second-line treatment. A comparison of the three measurement parameters (ovarian volume, follicle stimulating hormone level and antral follicular count) was made between these groups.

## DISCUSSION

Ovarian functional capacity is folliculogenesis and steroidogenesis 10-12 and the ovarian reserve is the total count of ovarian primordial follicles in a specific stage of a woman's life. The human ovary acquires its functional capacity during embryonic development. Oogenesis is genetically determined and at birth the woman has a certain number of primordial follicles that constitute the ovarian reserve that decrease

during the reproductive life 21. The ability to conceive is known as reproductive potential; its decrease is temporally correlated with the loss of follicles and reduction of oocytes, which reduce the ovarian reserve 22. To evaluate the ovarian reserve indirectly, 23 hormonal levels and transvaginal ultrasound are accessible 24,25. The basal determination of FSH; days 3 to 5 of the menstrual cycle is a useful indicator of ovarian reserve 26 its elevation is associated with alterations of the proliferative phase and inability to regulate folliculogenesis and follicular maturation. Basal concentrations higher than 12 IU / mL are related to ovulatory dysfunction and short luteal phase, and lower quality of ovules 27. The clomiphene citrate test and measurement of FSH, consists of the administration of 100mg of clomiphene citrate. days 5 to 9 of the menstrual cycle and measurements of FSH on day 3 21,27. The determination of the AMH; member of the family, Beta-type growth factor (TGF-beta) is expressed in preantral (<8mm) and antral follicles; its levels reflect the follicular reserve and it is the best biomarker of ovarian function independently of the patient's clinical situation 28,29.

Antral follicular count: Transvaginal ultrasound is used to determine the number of antral follicles that measure from 2 to 10mm in diameter; There is a positive correlation between the age of the patient and the ovarian volume, which decreases after 35 years of age 29.

The preservation of the ovarian reserve with the use of gonadotropin-releasing hormone analogues (a-GnRH) is controversial, as is the method of contraception during oncological management 21. Oncological management with Qt has secondary effects on patients such as; cardiotoxicity, leukemia and myelodysplastic syndrome, neutropenia, cognitive dysfunction, menopausal symptoms and ovarian failure and others. Qt causes loss of primordial follicles and ovarian atrophy 8. Oocyte death by apoptosis was identified as the main mechanism responsible for the loss of germ cells and premature ovarian failure Clinically, the impact of Qt on ovaries varies from none, to through different levels of partial damage resulting in reduced fertility, to damage with total loss of primordial follicles, ovarian atrophy and complete ovarian failure; the ovarian reserve occurs naturally with age, and Qt leads to ovarian failure early 9,16

The use of Qt in patients of reproductive age with breast cancer; mainly in women under 38 years 30,31

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the schemes such as cyclophosphamide, methotrexate, 5-fluorouracil or 5-fluorouracil, epirubicin, cyclophosphamide; they cause amenorrhea in 40% of children under 40 years and 76% in those older than this age; the use of taxanes increases the risk; 51.4% reported damage with docetaxel, doxorubicin, cyclophosphamide versus 32.8% with 5-fluorouracil, doxorubicin, and cyclophosphamide 32. The pelvic Rt affects the ovarian primordial follicles by apoptosis and develops premature ovarian failure; But, undamaged follicles can experience normal maturation; ovarian fibrosis and ischemia due to sclerosis do not favor optimal follicular development; ovarian function depends on the total dose, radiation field and age of the patient 33,34; oocytes are highly sensitive to radiation, and LD50 (radiation dose needs to kill half the total number of oocytes) was estimated at 4 Gy, recently 35 the lower dose is 2 Gy; women of reproductive age are less sensitive to gonadal damage due to greater follicular reserve, 20Gy are needed during childhood, compared to patients over 40 years of age, who already have a reduced ovarian reserve and only 5 to 6 Gy develop permanent ovarian failure; In addition, endometrial, myometrial atrophy, subepithelial fibrosis and decreased uterine vascularization occur 35,37.

The studies carried out so far are inconclusive regarding the role of tests for ovarian reserve in patients treated for breast cancer, first, data on different Qt regimens, number of patients involved 37. The Qt containing cyclophosphamide and taxanes cause greater gonadal damage 12,38; the approach of oncological management with less gonadal damage, and greater survival allows fertility 39 and Qt is stratified by the associated risk of ovarian insufficiency, in low, high and intermediate, see table 1.

Cyclophosphamide is a drug from the group of alkylating agents most used in breast cancer; Rt at high doses causes damage to certain organs in constant mitosis such as the gonads, can interrupt the functioning of the hypothalamic-pituitary axis and cause ovarian failure; it is possible that our study has no statistical differences between the groups of Qt and Rt related by the small number of patients, where most are of reproductive age with advanced breast cancer (stages II A and III A), and without medical information with regarding the possibility of conservation of fertility and the need for immediate treatment; it is proposed to implement in our hospital and nationally individual

measures of preservation of fertility when indicated; as reported in our study, 100% of patients were treated with oncological management without taking into account the reproductive aspects as is done in most hospitals due to lack of information 27,32

Fertility is reduced after oncological management; although, spontaneous pregnancies can occur; however, the low ovarian reserve, nor the regular menstruation is equivalent to fertility and the evaluation of the ovarian reserve must be done early in those patients of reproductive age who wish to form to conserve fertility.

Regardless of the type and dose of Qt or oncological management received, they will present ovarian dysfunction. Another aspect of importance for the quality of life of women with breast cancer is the psychological impact of patients, who require support groups, in conjunction with therapies focused on them; because some patients do not accept oncological management, with Qt, Rt or radical surgery; although, patients of reproductive age at the time of diagnosis, the prognosis worsens 39.

The ideal marker should be able to simultaneously assess the qualitative and quantitative aspects of the ovarian reserve. The biochemical variables include follicle-stimulating hormone (FSH), estradiol (E2), antimullerian hormone (AMH), the 3D ultrasonographic variables are the antral follicle count (AFC), ovarian volume, flow index (FI), vascularization index (VI) and vascularization Flow index (VFI), 33,34,35,36. In our hospital we do not have some of these tests nor are they routinely accessible; unlike other tests such as FSH levels and evaluation of the follicular score 6,7,9,20 by transvaginal ultrasound, which we used for this study. The world literature is controversial regarding the specificity and sensitivity of the tests to determine the ovarian reserve 23,25,30,31,32, good results have been obtained regarding the accuracy of the basal follicular count and ovarian volume by ultrasound transvaginal which is a minimally invasive study, but, operator dependent and the FSH results are significant when the two tests are compared and more sensitive, although, it is necessary to perform studies in a larger number of patients to estimate accurate results; some reports determine a level of FSH > 20mIU / ml as a cut-off point for the diagnosis of ovarian failure (related to ovarian reserve), in others the cut-off point is from 40 mIU / ml, mainly for the diagnosis of menopause

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37, in this study the cut of less than 20 mIU / ml was used to determine an adequate ovarian function and good ovarian reserve. Alternative therapies to prevent minor ovarian damage are multiple worldwide and scarce nationally 30-32. In our environment, oncological management focuses more on survival for patients with breast cancer; but, currently, it is important to implement preventive measures, offer information with medical evidence; to improve the quality of life including reproductive aspects in women of reproductive age 13,15 individually; The development of ovarian failure will cause an increased risk of chronic degenerative diseases in an early age of the woman's life, increasing morbidity and mortality, and the cost of health.

### FUTURE PERSPECTIVE

The risk of infertility due to Qt has improved in recent years and the ovarian reserve tests assess the damage; improving the knowledge about infertility as a potential risk of oncological management, allows to recommend techniques for the preservation of fertility in women at risk. Fertility counseling should be individual, the impact of Qt, ovarian reserve, the success of fertility preservation techniques are closely related to age, ovarian reserve, type and dose of Qt. The advances in the mechanisms by the chemotherapy that damages the ovarian reserve open new perspectives for the preservation of the fertility, with medicinal protection of the ovarian reserve; the majority is experimental; However, it is necessary to demonstrate that these agents do not interfere with the efficacy of oncological management or in reproduction 37-39.

### CONCLUSIONS

In recent years, prolonged survival and better quality of life in patients with breast cancer, the issue of fertility must be defined, and requires individual information about the damage and the preservation of future fertility.

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**Citation:** Vargas Hernandez Víctor Manuel, Ventura Quintana Valeria, Jose Maria Tovar Rodriguez, Victor Manuel Vargas Aguilar. *Ovarian Reserve and Breast Cancer. Archives of Reproductive Medicine and Sexual Health . 2018; 1(2): 17-25.*

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