Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 5 Issue 4 April 2023

Research Article

Fertility Preservation: Opinion of a Group of Experts

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DOI: 10.31080/ASWH.2023.05.0495

Received: June 17, 2022

Published: March 31, 2023

Abstract

Fertility preservation is the application of medical and laboratory strategies to preserve parental genetic offspring in adults or children at risk of sterility.

Cancer is the main indication of fertility preservation in patients of reproductive age. In recent decades, the incidence of cancer in adolescents has increased. Cancer treatments have also improved significantly, making cure possible today in a large percentage of patients. Most children and adolescents with cancer become long-term survivors, increasing interest in the effects of cancer treatment on fertility.

Social, economic and cultural conditions are also decisive in deciding when a couple seeks to promote their fertility.

Furthermore, other pathologies or even drugs for the prevention of rejection of transplanted organs can affect fertility and, therefore, such patients are susceptible to guidance on fertility preservation.

Success in assisted reproduction programs and cancer treatments provide alternatives to preserve fertility.

In this first Opinion of the Group of Mexican Experts on Fertility Preservation, we have evaluated oncological patients who are candidates for fertility preservation: young people at risk of compromising their fertility due to oncological treatment, but with sufficient ovarian reserve and acceptable vital prognosis. Special cases such as social preservation were also considered, in cases of different sexual conceptualization, as well as the basic legal and ethical aspects.

Keywords: Fertility Preservation; Cancer Treatment; Cryopreservation; Freezing; Oocyte; Ovarian Tissue Transplantation; Cancer Survivorship; Gonadotoxicity; Premature Gonadal Failure

Introduction

Fertility preservation (FP) could be defined as the application of medical and laboratory strategies in order to preserve the parental genetic offspring in adults or children at risk of infertility [1].

Cancer is the pathology that most frequently motivates the preservation of fertility in patients of reproductive age. In the last 30 years, the incidence of cancer in adolescents (15 to 18 years old) has increased, mainly at the expense of carcinomas, lymphomas and tumors derived from germ cells. But also the results of cancer treatments have improved significantly in the same three decades, so that today it is possible to obtain a cure in a large percentage of patients, with differences according to the type of cancer and the initial extension at the time of treatment. diagnosis. More than 80% of children and adolescents with cancer become long-term survivors, raising interest in the long-term effects of cancer treatment on fertility [2-4].

Social, economic and cultural conditions have also played an important role in being determinants for women to seek to delay more and more the moment of promoting her fertility in order to achieve personal, professional, social, economic goals, etc. [2-4].

And finally, other pathologies that are not so frequent, but not less important for that, such as Systemic Lupus Erythematosus (SLE), scleroderma, Rheumatoid Arthritis (RA), Wegener's granulomatosis or even the use of drugs to prevent rejection. of transplanted organs has a role in affecting fertility and therefore, such patients are susceptible to guidance on fertility preservation [2-4].

Fertility preservation is a discipline that has developed in the last two decades due to the success of both highly complex assisted reproduction programs and cancer treatments, providing an alternative to those women who need to preserve their fertility for the future. using cryopreservation techniques.

In this First Mexican Consensus on Fertility Preservation we have concentrated our efforts on evaluating who are candidates for fertility preservation and what type of technique to use: young patients in whom there is a risk that their fertility may be compromised in the near future due to at age, medical treatment, surgery and/or procedure that causes ovarian failure, but who at the same time are patients in whom their follicular load or evaluation of their ovarian reserve is still sufficient, and who have an acceptable vital prognosis.

Methodology

Two general objectives were set for the medical community, mainly obstetrician-gynecologists, reproductive biologists, oncologists, pediatricians and primary care physicians:

- Provide doctors with basic guidelines so that they have tools that allow them to provide adequate, timely and precise advice for each situation, in general and in particular, to young patients with cancer pathology. For this, knowledge of the effects of both the pathology they suffer from and the treatments that must be carried out with an effect on the gonads must be taken as a fundamental tool; as well as the possibilities and current results of the different fertility preservation alternatives.
- Develop an inter-institutional and specialist network in order to disseminate these concepts.

For patients, the objective is to provide information that guides about a particular oncological pathology and strategies to prevent damage to their immediate or future reproductive potential, whether due to the disease, as a consequence of the therapies used for its treatment or due to the pass of the time. In no case is the objective to replace the need to seek advice from a trained and certified doctor to guide the patient on the best possibilities of preventing damage to her reproductive potential.

The participants in this consensus were selected based on their experience and recognized prestige in the scientific community of our country. In order to be able to cover the different aspects related to this topic, the participants in this First National Consensus on Fertility Preservation were divided into ten work groups, each one focused on a specific topic. Each table was made up of 3 gynecological reproductive biologists, 3 gynecological oncologists and an embryologist.

Prior to the face-to-face meeting, the most recent bibliography was distributed among the participants, as well as the one considered by the coordinators to be the most relevant to the objectives of the consensus. All the participants received the complete bibliography and knew in advance the table that had been assigned to them. At the same time, a form was sent with all the points to be discussed in each work table and that were considered important for the consensus. Each of the participants was free to comment on them with the coordinator and, by mutual agreement, those they considered appropriate were added or deleted.

During the day of face-to-face work, a discussion time was granted for all the tables. In each of them, the coordinator was free to discuss in greater or lesser depth any specific theme or topic that he believed appropriate. The coordinator organized the points of view of the participants (oncologists, biologists and embryologists) of each of the topics discussed at his table, until reaching consensus.

Subsequently, a joint session was held with all the members of the consensus in which the coordinator of each table presented the conclusions that were debated by all the participants. All comments, suggestions or corrections were included in the final text after the majority agreement of the global participants.

Working tables

Women of childbearing age with gynecological cancer: Cervical Uterine Carcinoma.

Coordinator: Dr. Salim Abraham Barquet Muñoz.

Women of childbearing age with gynecological cancer: Endometrial Cancer.

Coordinator: Dr. Luis Arturo Hernández López.

Women of childbearing age with gynecological cancer: Ovarian Cancer.

Coordinator: Dr. Francisco José García Rodríguez.

Women of childbearing age with gynecological cancer: Cancer of the mammary gland.

Coordinator: Dr. Robin Jennifer Shaw Dulin.

Cancer in Girls and adolescents.

Coordinator: Dr. Patricia Cortes Esteban.

Women of childbearing age with non-gynecological cancer.

Coordinator: Dr. Benito Sánchez Llamas.

NON-ONCOLOGICAL PRESERVATION: Social and different sexual Conceptualization: indications and contraindications.

Coordinator: Dr. Efraín Pérez Peña.

NON-ONCOLOGICAL PRESERVATION: Social and different sexual conceptualization: ethical aspects.

Coordinator: Dr. Carlos Salazar López-Ortiz.

Below are the recommendations of the panel of Mexican experts on fertility preservation.

Women of childbearing age with cervical-uterine carcinoma.

Cervical-Uterine Carcinoma (CC) is one of the most common malignant neoplasms among women in low- and middle-income countries [2]. In Mexico, it ranks third in incidence after breast cancer and thyroid cancer [5].

About 40% of cases of this neoplasm are diagnosed before the age of 45. The survival of patients with Cervical-Uterine Carcinoma is increasing due to early detection and improvements in treatment; For this reason, the importance of including fertility aspects in the comprehensive management of patients with Cervical-Uterine Carcinoma and who do not have a satisfied parity is indisputable [3].

Staging of cervical-uterine carcinoma

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) established that Cervical-Uterine Carcinoma could be staged clinically and by imaging, with pathology evaluation in early stages being essential [6].

Recommendation

For the early stages, it is recommended to base the staging on the revision of the cone. Likewise, to rule out more advanced stages, clinical and imaging staging is recommended.

Standard treatment

Cervical-Uterine Carcinoma for treatment purposes can be divided into early stages, which includes stages IA to IB2 and IIA1 (tumors smaller than 4 cm); locally advanced stages, which are IB3 to IVA and the metastatic stage or IVB [7].

Early stages

In early stages, treatment is mainly surgical. The treatment of Microinvasive Cervical-Uterine Carcinoma (IA1 and IA2) consists of performing an extrafascial hysterectomy, with or without performing Bilateral Pelvic Lymphadenectomy depending on the status of Lymphovascular Permeation [8]. In non-microinvasive Cervical-Uterine Carcinoma (IB1, IB2 and IIA1), surgical treatment consists of radical hysterectomy with Bilateral Pelvic Lymphadenectomy [8].

Recommendation

Surgical treatment should be considered only in early stages.

Risk of recurrence

The American Joint Committee on Cancer points out that the most important risk factor for recurrence in Cervical-Uterine Carcinoma is lymph node involvement, describing that in stages IB the probability of pelvic lymph node involvement is up to 20% [9,10]. Patients in early stages who underwent radical hysterectomy with Bilateral Pelvic Lymphadenectomy and with lymph node involvement have a higher percentage of recurrence compared to those who do not (74.4% vs 85.6%, p = 0.04) [11]. It has been reported that patients in stages IA2 to IIB with lymph node involvement had lower overall survival (61% vs. 94%, p = 0.0001) and shorter disease-free period (46% vs. 92%, p = 0.0001) compared to who had no lymph node involvement [8].

Depending on the recurrence risk factors present, adjuvant therapy will or will not be indicated (Table 1]. Intermediate risk patients are considered to be those whose pathological findings are the presence of tumors larger than 4 cm, with Lymphovascular Permeation and that invade more than 1/3 of the stroma. These patients should be given adjuvant radiotherapy [12]. Patients at high risk of recurrence are considered to be those with pathological findings of lymph nodes with metastases, positive margins, and parametrial involvement. These patients will benefit from concomitant radiotherapy and chemotherapy, as adjuvant treatment [12].

Recommendation

Always discuss with the patient that there are risk factors for recurrence that require adjuvant administration, and that it can affect the fertility of patients.

Risk	Criteria	Adyuvance
Low risk. Must comply with all.	No lymphovascular permeation Depth up to 1/3 of the stroma Tumor size < 2 cm	None.
Intermediate risk. Must meet two out of three.	With lymphovascular permeation Depth of invasion > 1/3 Tumor size > 4 cm	Teletherapy with brachitherapy.
High risk Must meet one of three	Nodal involvement Positive margin Positive parameters	Chemotherapy and radiotherapy. concomitant with brachytherapy

Table 1: Pathological factors that indicate recommendation of adjuvant therapy [7].

Effect on fertility according to treatment by stage

LPB can cause postoperative morbidity in patients, such as the presence of lymphoceles in up to 20%, and their effect on fertility is unknown. Adhesion formation following OLP may also have an impact when the uterus is preserved [13].

Radiotherapy, regardless of its modalities, has a deleterious effect on reproductive and ovarian function. The therapeutic doses required in the treatment of Cervical-Uterine Carcinoma range from 75 - 85 Gray [7]. Ovarian failure occurs with exposure to 6 Gray. However, there are other associated factors such as age (odds ratio (OR) 1.8, $p < 0.001$), radiotherapy to the pelvis (OR 25.4, $p < 0.001$) and doses greater than 10 Gray [14]. The uterus ceases to be functional with exposure to 25 Gray [15]. The effect of radiotherapy on the uterus is translated into a decrease in its size, fibrosis, atrophy, and myometrial and endometrial ischemia. This can interfere with embryo implantation, increasing the risk of miscarriage or premature delivery. With doses >10 Gray, the risk of preterm birth (OR 3.5, 95% CI 1.5-8.0; $p = 0.03$), low birth weight infants (OR 6.8, 95% CI 2.1-22.0, $p = 0.001$) and small-for-gestational-age infants (OR 4.0, 95% CI 1.6-9.8; $p = 0.003$) [16].

Chemotherapy can also damage ovarian function through different mechanisms and, additionally, this damage will depend on the regimen and the applied dose (Table 2). The regimens studied, preferably when neoadjuvant therapy is used, are with platinum agents at non-therapeutic doses and taxanes. The effect on ovarian function, much less on reproductive function, is not known.

Chemotherapeutic agent	Risk of gonadotoxicity	Mechanism of action
Alkylating Agents: Cyclophosphamide. Ifosfamide.	High	Induces chain breakage of Deoxyribo Nucleic Acid (DNA). Affects primordial follicles.
Platinum: Cisplatin. Carboplatin.	Intermediate	It induces chromosomal damage and DNA damage.
Taxanes: Paclitaxel.	Intermediate	It inhibits microtubule formation and meiotic spindle function.
Anthracyclines: Doxorubicin.	Intermediate	It inhibits DNA replication and transcription.
Antimetabolites: Gemcitabine. 5-fluoroacyl.	Low	It acts on cells that synthesize DNA.

Table 2: Cytotoxic agents [17].

Recommendation

Regardless of the stage in which the Cervical-Uterine Carcinoma occurs, it is essential to take into account that the standard treatment will always definitively affect the fertility and ovarian function of the patient.

Initial evaluation to preserve fertility according to stage

It is essential to know the desire to preserve fertility to establish an adequate evaluation and fertility-preserving treatment. Once the patient's desire to preserve her fertility is confirmed, the reproductive biologist should start the ovarian reserve study to properly guide the patient. This may be done concurrently with the rest of your oncology evaluation. The histopathological types that may be candidates for fertility-sparing treatment are epidermoid, adenocarcinoma or adenosquamous. The rest of the histopathological types (neuroendocrine or gastric-type adenocarcinoma), due to their aggressiveness and high risk of recurrence, are not candidates for organ preservation [18].

The initial evaluation requires evaluating the tumor size, as well as the depth of invasion and involvement of other organs, especially the lymph nodes. For this, magnetic resonance imaging (MRI) is the best tool [19]. Its diagnostic accuracy for tumor size is a sensitivity of 65% (57-72%), a specificity of 96.5% (95.1-97.6%), a positive predictive value of 77.3% (69.2-84.1%) and a predictive value negative of 93.8% (92 - 95.3) [20]; to establish the depth of invasion, it has a sensitivity of 16.7%, specificity of 95.3% (93.8 - 96.5%), and positive and negative predictive values of 7.8% (2.2 - 18.9%) and 97.9% (96.8 - 98.7%) , respectively. PET/CT (computed tomography) can be used for lymph node evaluation or distant involvement [21].

Recommendation

- Fertility preservation treatment should not be started until the oncologist has confirmed that the patient is a candidate for this option.
- The role of MRI is for the initial evaluation of tumor size, depth of invasion and involvement of other adjacent organs. PET/CT may be helpful in evaluating whether there is nodal or distant disease.

Treatment by stage to preserve the organ

All patients with reproductive desire must undergo highly complex assisted reproduction techniques to obtain and cryo-preservation of eggs, prior to oncological treatment. It is important to emphasize to patients that, despite preserving the uterus and ovaries, only 90% of fertility is preserved, since when intermediate or high risk factors for recurrence are present, radiotherapy or chemotherapy are required. and concomitant adjuvant radiotherapy.

Ideal candidates are patients with stages I A 1, I A 2, and I B 1. In patients with stages I B 2 and I B 3, the evidence on potential reproductive benefits is scant. Recurrences of up to 6.3% with a cancer mortality of 1.3% have been reported in this group [22].

In locally advanced stages, the uterus cannot be preserved, therefore, and until now, there is no possibility of pregnancy. The alternative is to preserve ovarian function through ovarian transposition. Reports of preservation of ovarian function with this type of technique range from 50% to 90% [23]. Other alternatives are the cryopreservation of ovules and/or ovarian tissue, or means still considered experimental such as ovary or ovarian tissue transplant to be used in the future, through assisted reproduction, with surrogate motherhood.

Recommendation

- In patients with stages I to 1 without Vascular Lympho Permeation, perform a cervical cone (preferably a cold cone, although it can be performed with a diathermic loop) with a margin of at least 5 mm. An endocervical curettage should be performed.
- In stages I to 1 with Vascular Lympho Permeation or stages I to 2, the ideal treatment is cold cervical cone with a pathological margin of at least 5 mm and Bilateral Pelvic Lymphadenectomy or sentinel lymph node; or, a radical trachelectomy with Bilateral Pelvic Lymphadenectomy or sentinel lymph node.
- In stage I B 1, the treatment of choice is radical trachelectomy with Bilateral Pelvic Lymphadenectomy or sentinel lymph node. This requires preserving the uterus and ovaries. The cervix is almost completely resected, leaving at least 5 mm of the cranial portion for the placement of a cerclage. Cerclage placement with a 0 non-absorbable suture is recommended, as well as a transcervical catheter for at least 3 weeks to avoid stenosis. The utero-sacral ligaments should be removed 1-2 cm from the cervix with preservation of the hypogastric nerve plexus. It is recommended to leave a vaginal margin of 1-2 cm.

The ureters must be dissected and completely separated from the cervix. Parametrial resection should be performed at the level of the ureteral bed, at least.

- In stage I B 2, the treatment of choice is radical trachelectomy with Bilateral Pelvic Lymphadenectomy.
- In stages I B 3, it is not recommended to preserve the uterus due to the increased risk of recurrence. The role of neoadjuvant treatment in this group of patients is being investigated.
- In locally advanced stages (I B 3 to II B), consider preserving ovarian function through ovarian transposition. It is not recommended in stages III or IV due to the high percentage of recurrence and low survival.

Women of childbearing age with endometrial cancer

Endometrial cancer (Ec) is the most frequent gynecological cancer in developed countries and the second in developing countries. In Mexico, 2,606 cases were reported in 2008, with a rate of 4.7/100,000 inhabitants [24].

It occurs most frequently in postmenopausal women, but 25% of cases are in premenopausal women and 3–5% in women under 40 years of age at diagnosis. In the group of young women with endometrial cancer, a history of ovarian dysfunction, anovulation, infertility, and obesity is often recognized.

In young women, endometrial cancer is usually of the well-differentiated endometrioid type, estrogen-dependent, with little tendency to invade the myometrium and associated with a good prognosis. For this reason, some well-selected patients with endometrial cancer may be candidates for conservative management with the intention of preserving fertility potential.

Diagnosis

The differential diagnosis between low-grade endometrioid adenocarcinoma and atypical endometrial hyperplasia is not easy, so the participation of expert pathologists is important for the proper selection of patients.

The diagnosis of endometrial cancer requires a high index of suspicion; Table 3 lists the clinical data that warrant targeted screening in high-risk patients and purposeful search for endometrial cancer in those with symptoms.

Patients in whom screening for endometrial cancer is warranted.	Patients in whom endometrial cancer should be excluded.
Postmenopausal; exogenous estrogens.	Genital bleeding in postmenopausal women.
Postmenopausal, obese; family history of endometrial, breast, colon, or ovarian cancer.	Pyometra in postmenopausal women.
Menopause after age 52.	Endometrial cells in postmenopausal cytology.
Premenopausal women with chronic anovulation.	Intermenstrual bleeding or hypermenorrhea in perimenopausal women.
Postmenopausal; exogenous estrogens.	Abnormal bleeding in anovulatory premenopausal women.

Table 3: Indications for research on endometrial cancer [25].

The tests available are:

- **Vaginal ultrasound:** Positive ultrasound increases the possibility of endometrial cancer from 14% to 31.3%; Negative US reduces the chance from 14% to 2.5% [26].
- **Office biopsy:** Positive biopsy represents an 81.7% chance of endometrial cancer; negative biopsy, a 0.9% possibility of endometrial cancer [27].
- **Hysteroscopy:** The positive result increases the possibility of cancer to 71.8%; the negative result reduces the possibility of endometrial cancer to 0.6% [27].

Recommendation

It is recommended to use transvaginal ultrasound if you have extensive experience, office biopsy and hysteroscopy; All three tests have shown high specificity in diagnosing the disease.

Standard treatment

Standard treatment for endometrioid carcinoma involves staging laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal lavage, and lymph node sampling when appropriate; 5-year survival in patients initially treated with this approach is approximately 94% [28].

The correct staging of endometrial cancer is critical to define the appropriate treatment. The prognosis is established based on the histological grade, depth of myometrial invasion, cervical involvement, involvement of the lymphovascular space, pelvic and para-aortic lymph node metastases, adnexal metastases, and positive peritoneal cytology (Table 4).

IA	Limited to the uterus, myometrial invasion <50%.
IB	Myometrial invasion >50%.
II	Cervical stromal invasion, but limited to the uterus.
IIIA	Invasion of the uterine serosa or adnexa (ovaries, salpinges, broad ligament).
IIIB	Vaginal and/or parametrial invasion
IIIC1	Positive pelvic nodes.
IIIC2	Positive para-aortic nodes.
IV	Distant metastatic.

Table 4: Surgical staging of Endometrial Cancer.

Modified from Soslow RA [28].

Effect on fertility according to treatment by stage

The obligatory effect of the standard treatment of endometrial cancer is the absolute loss of reproductive potential precisely because the diseased organ is the reproductive organ per se; likewise, staging surgical treatment requires the simultaneous removal of both ovaries.

The Committee of the International Federation of Gynecology and Obstetrics for ethical aspects in human reproduction and women's health has indicated that, in women with cancer, the treatment of the disease is the primary medical objective and that the risks associated with any deviation or delay of established standard treatments should be carefully evaluated and should not have a significant impact on treatment [29].

Therefore, patients who are candidates for conservative management of endometrial cancer should be carefully selected with imaging methods and endometrial sampling, considering that surgery will not be performed.

There is no optimal method for evaluation prior to conservative treatment, so it is necessary to use several non-invasive or minimally invasive indirect diagnostic methods to try to obtain a "clinical staging" of patients in whom it is decided to preserve fertility by conserving the uterus [30].

Routine blood and urine tests, including CA-125 levels, should be performed, since elevation of this marker could suggest advanced disease. Different radiologic evaluation modalities can be used to improve the accuracy of clinical staging. Transvaginal ultrasound, Computed Tomography and Magnetic Resonance Imaging have been compared for the evaluation of the primary tumor, without relevant differences having been described in terms of their usefulness and accuracy [31]. However, MRI with contrast has shown superiority in the evaluation of myometrial invasion, over non-contrast, Computed Tomography and Ultrasound [31].

Recommendation

Conservative treatment should only be offered to patients with well-differentiated grade 1 tumors, without invasion of the lymphovascular space, without evidence of myometrial invasion, metastatic disease or adnexal tumors, and with expression of progesterone receptors in the endometrium.

Measures to preserve fertility according to stage.

The evaluation of patients who are candidates for conservative treatment must include 3 strict criteria [32].

(Figure 1):

- Hysteroscopic evaluation of the neoplasm, with special attention to its size (≤2 cm), location and absence of endocervical extension.
- The patient's desire to become pregnant, considering 18 months as the maximum safety period to become pregnant before proceeding with definitive oncological treatment.
- Evaluation of the ovarian reserve, considering that pregnancy must be achieved through highly complex assisted reproduction techniques.

Hysteroscopic evaluation is the best method for evaluating the primary neoplasm (to avoid clinical understaging errors) and the best method for monitoring and evaluating response to treatment [27]. Tumor size is included among the evaluation elements based on "larger tumor size, less possibility of response to treatment" and "the larger the tumor, the greater the risk of recurrence".

The evaluation of the ovarian reserve must be carried out under baseline conditions, before starting progestogen treatment, to

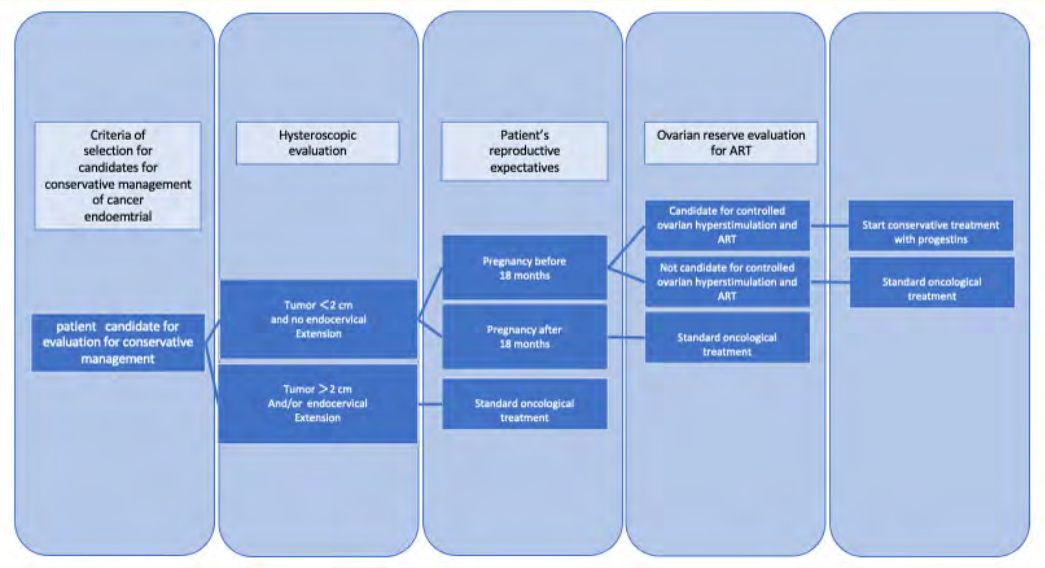

Figure 1: Comprehensive evaluation of patients with endometrial Ca and candidates for conservative fertility-preserving treatment. 1st Mexican National Consensus on the Preservation of Fertility in Women.

*Hormones (day 3-5 of the cycle or randomly if amenorrhea): FSH, LH, estradiol, prolactin, free testosterone, total testosterone, androstenedione, TSH, Anti-Müllerian Hormone, insulin, fasting glucose.

exclusively select women who can subsequently undergo assisted reproduction in order to increase the possibility of early pregnancy.

Recommendation

- Use hysteroscopy to evaluate the primary neoplasm and to monitor and evaluate the response to treatment.
- It is essential to carry out definitive surgical oncological treatment of endometrial cancer once the objective has been achieved (pregnancy) or the attempt has failed (no satisfactory response to treatment in no more than 18 months or no success in conceiving).
- When the clinical evaluation is not conclusive, a complete laparoscopic evaluation with peritoneal cytology, pelvic lymph node sampling and adnexal review should be considered before deciding on conservative treatment.

Table 5 shows the selection criteria for evaluating candidates for conservative treatment of endometrial cancer recommended by this consensus.

Age less than 45 years.
Well-differentiated endometrioid carcinoma, grade 1, in an adequate histological specimen.
Absence of lymphovascular invasion in adequate histological specimen.
Intense and diffuse expression of progesterone receptors in adequate histological specimen; positive estrogen receptor expression (regardless of intensity level).
Maximum 4 weeks elapsed from the date of taking the endometrial biopsy.
No evidence of myometrial invasion on magnetic resonance imaging (MRI) with contrast.
No evidence of metastatic disease on contrast-enhanced computed tomography (CT).
No evidence of suspicious adnexal tumor on transvaginal ultrasound or CT.

Table 5: Selection criteria for evaluating candidates for conservative treatment of endometrial cancer.

Fertility-preserving cancer treatment schemes

Current options for fertility preservation are limited to hormonal treatments. Patients who decide to opt for hormonal conservative treatment should be widely warned about the potential risks, since to date the optimal progestin treatment has not been scientifically proven. Response to treatment can vary, depending on tumor receptor status, from 26-89% in tumors positive for estrogen receptors (ER) and progestational receptors (PR) to only 8-17% when receptors are negative [33].

Varying doses of different progestational agents have been tried. Medroxyprogesterone acetate (MPA) at doses of 100-800 mg/day, megestrol acetate (MA) at doses of 40-160 mg/day, and the combination of tamoxifen with progestin have given similar results. 62-75% of patients with clinical stage I and well-differentiated adenocarcinoma respond adequately to progestational treatment for 3-9 months and most achieve long-term responses; however, the absence of PR could affect the success of the treatment [33].

Kalogiannidis., *et al*. in 2011 published the results of a review of studies that included patients treated with medroxy-progesterone acetate or megestrol acetate, evaluated by endometrial biopsy every three months. The overall response rate was 73% (median 4 months, range 1-15 months) and the relapse rate was 36% (median follow-up 22 months, range 6-73 months). Overall, 40% of patients who achieved satisfactory responses achieved a subsequent pregnancy, half of them through assisted reproduction treatments [34].

There are few data with high statistical power that establish the type of progesterone, route of administration or dose, since the information on the efficacy and toxicity of progestogens in endometrial cancer is limited, the studies come from meta-analyses, observational studies, series and case reports including different doses, drugs and regimens. The Spanish Society of Gynecology and Obstetrics establishes that the progestins to be used must be medroxy progesterone acetate or megestrol acetate [35]. Additional studies and adequate follow-up are still required to define the usefulness of the levonorgestrel-releasing intrauterine device (LNG-IUD).

Patient follow-up should include serial transvaginal ultrasound, endometrial biopsies, and CA-125; Periodic sampling of the endometrium should be done every 1 to 6 months. To date, the time required for treatment to obtain a response and the duration of the response have not been established; Some publications suggest that the minimum treatment time needed is 3.6 months and that treatment should be maintained for at least 5.4 months [36]; most studies repeat a biopsy after 3 months of hormonal treatment, while the duration of treatment varies from 15 to 35 months [35].

Recommendation

It is suggested to adhere to one of the following treatment schemes:

- Medroxy-progesterone acetate, 500 mg/day, orally, daily, without interruption.
- Megestrol acetate, 160 mg/day, orally, daily, without interruption.
- Combined treatment with one of the above progestagens plus levonorgestrel-releasing intrauterine device (LNG-IUD).
- Levonorgestrel-releasing intrauterine device (LNG-IUD) only (only under inclusion in prospective protocols evaluating "non-inferiority" against other treatment schemes).

Evaluation of response to treatment should be by hysteroscopy, according to the following guidelines:

- Perform hysteroscopy at intervals of 0 (pre-treatment), 3, 6 and 9 months.
- Characterize the neoplasm (and record in the file) in terms of:
- Location,
- Largest diameter size,
- Width of the base (if applicable in pedunculated lesions),
- Hysteroscopic appearance (with obtaining a photographic image).
- Complete tumor response: no identifiable tumor.
- Partial tumor response: tumor size reduction greater than or equal to 30%.
- No tumor response: size and appearance identical to pre-treatment.
- Tumor progression: growth in volume or extension greater than or equal to 15%.

- In case of complete tumor response, proceed to histological confirmation:
- Obtain four directed biopsies from the original location of the tumor.
- Cover an area of 4 ± 2 square centimeters to take the biopsies.
- If any of the biopsies are positive for adenocarcinoma, return to treatment and prolong the following 3 months.

Figure 2 shows the decision flowchart for the conservative treatment of women with endometrial cancer suggested by the panel of experts.

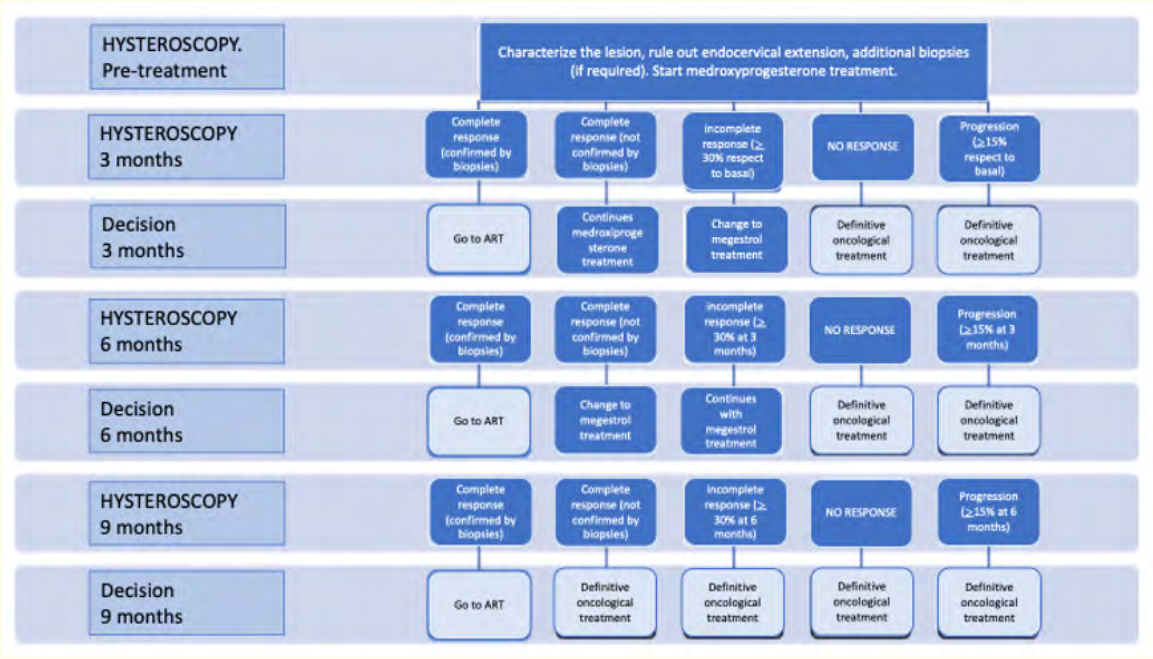

Figure 2: Decision flowchart for conservative treatment of endometrial cancer. 1st Mexican National Consensus on the Preservation of Fertility in Women.

Safety of conservative management of endometrial cancer

Endometrial cancer in patients younger than 45 years is less common, but apparently has a better prognosis than in older patients. However, endometrial cancer detected at a young age increases the risk of cancer associated with Lynch Syndrome/ Hereditary Nonpolyposis Colorectal Cancer (HNPCC), as well as the possibility of synchronous or metachronous ovarian cancer unrelated to Lynch Syndrome/Nonpolyposis Colorectal Cancer. hereditary polyposis. When patients with stage 1 endometrial cancer are evaluated, the occurrence of ovarian metastases is rare (< 5%), but the incidence of endometrial cancer at any clinical stage with synchronous ovarian cancer is 10 to 29.4% [37].

Even though the degree of histological differentiation is a sensitive indicator of the risk of tumor spread, 2.8% of grade 1 lesions present with pelvic lymph node involvement and 1.7% para-aortic; 10% of grade 1 tumors have deep myometrial penetration, 6% of occult stages 1 and 2 tumors have spread to adnexa, and 19% of patients may have coexisting ovarian tumors [38].

Recommendation

- In young patients with endometrial cancer, genetic counseling is recommended to rule out the presence of Lynch syndrome
- In the event that there is a diagnosis of Lynch Syndrome, it is recommended to ensure the absence of a double primary, especially a synchronous ovary.

Reproductive treatment strategies for conservatively treated patients with endometrial cancer

The safety of assisted reproduction treatments in patients with a history of gynecological cancer has been a cause for concern, although several studies have provided reassuring information. Ovarian stimulation does not seem to be associated with an increased risk of relapse and subsequent pregnancies do not worsen the oncological prognosis [39]. The impact of elevated estradiol levels on endometrial cancer is uncertain, and very little information is available about the protocol, duration, or number of ovarian stimulation attempts in patients with early endometrial cancer.

There are strategies to keep estradiol levels low during controlled ovarian stimulation, so that patients with estrogen-dependent cancers remain safe and tumor recurrence is not increased. Some studies with breast cancer patients have shown that the use of aromatase inhibitors combined with gonadotropin-releasing hormone agonists to trigger ovulation, instead of human chorionic gonadotropin, can reduce estrogen exposure and the incidence of ovarian hyperstimulation syndrome. Triggering with gonadotropin-releasing hormone agonists can result in a greater number of mature oocytes and, with this, a greater number of oocytes and/or embryos to cryopreserve, compared to cycles with human Chorionic Gonadotropin [40].

On the other hand, recent evidence indicates that in the same menstrual cycle there may be multiple waves of recruitment of dominant follicles and that, therefore, the concept of a narrow window of opportunity for follicular recruitment could be erroneous. Thus, the current availability of Gonadotropin Releasing Hormone antagonists combined with the discovery of multiple recruitment waves have allowed the advent of random-start controlled ovarian hyperstimulation (random-start HOC) in the late follicular phase or in the luteal phase of the menstrual cycle for embryo cryopreservation in cancer patients. Unfortunately, the literature on late follicular phase or luteal phase initiation of controlled ovarian hyperstimulation and "emergency" fertility preservation is still limited to case series, although its use is increasing [41].

The American Society for Reproductive Medicine (ASRM) recently reviewed the evidence on fertilization and pregnancy rates achieved after oocyte vitrification and devitrification. Published figures show similar results to those obtained when fresh oocytes are used in cycles of *In Vitro* Fertilization / Intra Cytoplasmic Sperm Injection. On the other hand, no increases in chromosomal abnormalities, birth defects, or developmental abnormalities have been observed when comparing the incidences of pregnancies achieved with *In Vitro* Fertilization/Intra Cytoplasmic Sperm Injection against those of the general population [42].

Recommendation

- The reproductive management after the response with progestins will depend on the diagnosis of infertility.
- The infertility specialist, the gynecologist oncologist together with the patient will make the decision for the optimal management.

Women of childbearing age with ovarian cancer

According to Globocan statistics for Mexico in 2018, ovarian cancer (CaO) ranked eighth as a cause of malignant disease in Mexican women, being the third gynecological tumor after Cervical-Uterine Carcinoma and Endometrial Cancer. 12.1% of ovarian cancer cases occur in reproductive age [2].

There are three families of ovarian cancer from the point of view of their histogenesis, epidemiology, natural history and frequency: epithelial tumors (80%), germ cell tumors (15%) and stromal tumors (5%) [43].

When approaching women with suspected ovarian cancer, borderline tumors and adnexal tumors must also be taken into account.

Diagnosis

Ovarian tumors are not amenable to timely detection or screening. The ideal method to identify them is pelvic or transvaginal ultrasound, although, in addition to detecting malignant tumors, it also detects adnexal tumors, which are very common in women over 40 years of age. The diagnosis of an ovarian tumor is through oophorectomy, since needle biopsies of cystic tumors are contraindicated due to the potential for dissemination; however, in this way many unnecessary surgeries would be performed that would disproportionately raise costs with little benefit and high morbidity [44,45].

Adnexal tumor

Standards have been proposed for the study of adnexal tumors, based on the premise that "ovarian tumors in prepubertal and postmenopausal women should be considered cancer until proven otherwise"; while an adnexal tumor in women of reproductive age has an 80% chance of being benign (cystic teratoma, functional cyst or endometrioma).

Recommendation

- Ovarian tumors can be managed with observation or conservative treatment, if they meet the following requirements:
- Women of reproductive age.
- They are purely cystic (not solid, without septa or vegetations).
- or Less than 10 cm.
- or one-sided.
- or no ascites.
- No data of acute abdomen due to torsion, necrosis or rupture.
- All tumors that do not meet these requirements are subject to surgical exploration, either open or laparoscopic.
- If it is necessary to intervene in a patient of reproductive age and with an adnexal tumor, it is recommended, as far as possible, to do it electively and not as an emergency, without the possibility of transoperative anatomo-pathological diagnosis.
- Hysterectomy with bilateral salpingo-oophorectomy should never be performed, regardless of the findings (transcoelomic spread, carcinomatosis, strong suspicion of malignancy).
- It is recommended to perform unilateral cystectomy or salpingo-oophorectomy and never perform wedge of the contralateral ovary.
- Fertility should never be compromised.

Borderline tumors

They are a particular group of tumors in which the neoplasm has a fundamentally intracystic growth and, despite invading the capsule and spreading to the peritoneum, the implants maintain the non-invasive characteristics of the original borderline tumor. They are not biologically aggressive, have little potential to invade and do not cause visceral metastases [46].

They are diagnosed as an adnexal tumor: they are heterogeneous tumors (cystic and solid, with/without vegetations inside and thick walls or septa) that can raise the CA 125 marker and do not affect the general condition. Conventional management is total abdominal hysterectomy with bilateral salpingo-oophorectomy, prior cavity lavage, peritoneum sampling, omentectomy, and diaphragm biopsies. Lymphadenectomy is very controversial. Survival is more than 90% at 10 years and, despite presenting dissemination, they are not managed with chemotherapy if the metastases are borderline [46].

Recommendation

- In women of reproductive age, conservative management is suggested, performing fertility-preserving unilateral cystectomy or salpingo-oophorectomy, although cystectomy has a higher rate of local relapse.
- Staging must be completed and the uterus and contralateral ovary must be kept intact (do not perform ovarian wedge).
- If there is bilaterality, remove the larger one with bilateral salpingo-oophorectomy and perform cystectomy on the smaller one.
- If possible, the ovarian tissue should be kept in physiological solution at room temperature and sent immediately to an assisted reproduction center in order to assess the possibility of cryo-preserving the ovarian tissue.
- When the patient completes her wishes for fertility, it is advisable to complete the oncological treatment.

Epithelial tumors

They are the most frequent and two subtypes with prognostic significance have been identified [47):

- High-grade serous papillary carcinoma: possibly originating in the fallopian tube, it is a biologically aggressive tumor with a mutation in the proapoptotic gene P53.

- Tumors originating from the adenoma-hyperplasia-borderline tumor-invasive carcinoma sequence. They are low-grade serous, mucinous, endometrioid and clear cell tumors (although the latter are considered biologically aggressive). Its evolution is less aggressive and the mutations originate in the K-ras, BRAF and PTen genes.

The age of presentation is usually above 45 years, more frequent in postmenopausal women, with low parity or nulliparity, prolonged menstrual life (incessant ovulation theory), and affects a particularly vulnerable group that are those patients with gene mutation BRCA 1 and BRCA 2, which suffer from it at younger ages, the most frequent type being high-grade papillary serous [48].

The only stage amenable to fertility-preserving unilateral salpingo-oophorectomy is stage I-A-1, which represents unilateral tumors, with an intact capsule, lavage, and negative staging. In cases I-B-1, bilateral tumors with intact capsule, negative lavage and staging, the uterus can be preserved.

The remaining stages, due to their aggressive nature and high recurrence rate, require total hysterectomy with bilateral salpingo-oophorectomy and complete staging routine that implies loss of reproductive potential.

Recommendation

- Prophylactic bilateral salpingo-oophorectomy is recommended in women over 35 years of age or at the end of the reproductive stage.
- When fertility has been preserved, suggest to the patient the possibility of performing a cycle of highly complex assisted reproduction with pre-implantation genetic diagnosis, which prevents the transmission of hereditary forms.

Germ tumors

These tumors are identified in girls, adolescents, and young women with a mean age of presentation of 19 years. They are divided into two groups: dysgerminoma and non-dysgerminoma (which includes immature teratoma, embryonal carcinoma, endodermal sinus tumor, and choriocarcinoma). They elevate markers such as lactate dehydrogenase (DLH), alpha feto protein (AFP), and beta fraction of human chorionic gonadotropin (β-hCG). They are mostly diagnosed in early stages [49].

Fertility management is conservative. They are chemo-curable tumors, whose survival rate reaches up to 90% [50].

Recommendation

- The intact removal of the tumor should be carried out, the tube should be preserved if it is not adhered and compromised, and a visual and palpatory staging with cyto-reduction should be performed, if warranted.
- Hysterectomy with bilateral salpingo-oophorectomy is not allowed.
- Oocyte cryopreservation should be considered in postmenarchal women and ovarian tissue cryopreservation in prepubertal girls who will undergo systemic management with chemotherapy due to the risk of damage to the germinal epithelium and premature ovarian failure.

Stromal tumors and sex cords

They represent an infrequent group that, however, can present in women in childhood and the early postpubertal stage, as well as in the reproductive stage. They are derived from the sex cords and ovarian stroma and are composed of various combinations of elements, including theca and granulosa cells, Sertoli and Leydig cells, and morphologically indifferent cells [51].

Up to 5% of granulosa cell tumors occur in the juvenile form and in prepubertal girls. In girls, 75% are associated with pseudo-sexual precocity due to estrogenic secretion and in reproductive age they are associated with menstrual irregularity and amenorrhea. They are associated with endometrial hyperplasia and endometrial cancer and rarely produce androgens and virilization. Most are diagnosed in stage I, so fertility-sparing surgery with contralateral ovarian and fallopian tube-conserving uterus can be considered [52]. Adjuvant chemotherapy is not given in stage I. More advanced stages require radical management. Surveillance must be close, since they can relapse from 5 to 30 years after diagnosis [53].

The management in relation to the reproductive future of patients with granulosa cell tumors is complicated by the hormonal production of tumor origin.

- For their part, Sertoli-Leydig tumors occur in women of reproductive age (third and fourth decades of life), and are low-grade tumors that produce androgens and virilization in 70-80% of patients. They are very rarely bilateral [54,55].

In Sertoli-Leydig tumors, since they are very rarely bilateral, conservative management of fertility with unilateral salpingo-oophorectomy is possible. There is no effective chemotherapy for them. Survival at 5 years is 70-90%. Adjuvant chemotherapy is recommended in patients with advanced stages, poor or intermediate differentiation, a retiform pattern, and the presence of heterologous elements [56].

Recommendation

- In stage I granulosa cell tumors, consider fertility-sparing surgery. In more advanced stages, cryopreservation of oocytes from the contralateral ovary is recommended prior to definitive management.
- Close monitoring should be done. For monitoring, the inhibin marker can be used.

Women of childbearing age with breast cancer

Breast cancer (BCC) is the most common tumor in the world, and represents the leading cause of death from cancer. 45% of cases occur in low- and middle-income countries [1].

In Mexico there has been a constant increase in incidence and mortality in the last three decades, and only between 2000 and 2013 the incidence has gone from 10.76/100,000 women older than 25 years to 26.1/100,00 [57].

In women of reproductive age, breast cancer is also the most frequently diagnosed malignant disease, but while in the United States 5% of new cases of breast cancer are diagnosed in patients under 40 years of age (11,160 cases per year), in Latin America the rate of breast cancer in young women reaches 10-15%. In addition, in Mexico, the mean age at diagnosis is 52.5 years, a decade lower than that reported in the population of the rest of North America and Western Europe [58].

Staging

Patients are staged according to clinical stage at presentation using the American Joint Committee on Cancer 8th edition TNM system [59]. Based on the classic parameters of tumor, lymph node status and metastasis (TNM), it is possible to determine a conventional clinical and pathological stage. By adding tumor grade, estrogen and progesterone receptor status, HER2 neu, and, if possible, the recurrence score calculated by Oncotype Dx, prognostic anatomic and pathologic stage can be established.

Conventionally, breast cancer is divided into early, locally advanced, and metastatic stages as follows:

- Early disease: CD 0, I, IIA, IIB (T2N1).
- Locally advanced disease: CD IIB (T3N0) IIIA to IIIC.
- Metastatic disease: CD IV (M1).

Survival at 5 years varies according to the clinical stage, from 95% when breast cancer is diagnosed in stage EC1 to 18% when the patient presents EC IV [2].

Recommendation

The incorporation of biomarkers is recommended to determine an anatomical and pathological stage, and establish a prognosis.

Treatment by clinical stage

Breast cancer treatment is constantly evolving and is nowadays highly personalized. The ideal scenario includes a multidisciplinary management where all the branches of oncology (surgeons, medical oncologists, radiation oncologists, pathologists, radiologists) come together to obtain the best possible result, with interdisciplinary decision-making that guarantees the best individualized treatment for each patient.

Treatment in early stages

In general, patients with early breast cancer undergo primary surgical treatment, offering local control either through conservative surgery or total mastectomy. Evaluation of the axillary status should be performed by means of Fine Needle Aspiration Biopsy (FNAB) [2].

Adjuvant systemic treatment is offered according to histopathological characteristics such as tumor size, grade, number of affected lymph nodes, estrogen and progesterone receptor status, and overexpression of HER2 neu.

After surgical treatment and the selection of local control measures (surgery, radiotherapy), the need to offer adjuvant systemic treatment with endocrine treatment, chemotherapy or biological treatment is determined according to the characteristics of the tumor and the lymph node status.

Recommendation

- Conservative surgery is always accompanied by adjuvant radiotherapy, being equivalent to total mastectomy in terms of oncological control. It allows to preserve the organ obtaining an acceptable cosmetic result with a low rate of recurrence. Conservative surgery is contraindicated in multi-centric disease, when there is a poor breast-tumor relationship, the presence of diffuse micro-calcifications, a history of having

previously received radiotherapy in the same area, in cases associated with pregnancy and in the presence of persistently positive margins.

- Patients who are not candidates for conservative surgery initially due to a poor breast-tumor relationship can be treated with neoadjuvant systemic therapy with the intention of inducing a response and improving the breast-tumor relationship.
- Total mastectomy is indicated in patients who are not candidates for conservative surgery initially or in patients who are not interested in preserving the gland. The possibility of immediate reconstruction should be considered according to the patient's preferences.
- Post-mastectomy radiotherapy is offered to patients with a high risk of recurrence, including tumors larger than 5 cm, positive deep margins and positive lymph nodes.
- The evaluation of the status of the axillary nodes should be performed by ultrasound-guided BAAF when the nodes are clinically or radiologically suspicious. If the BAAF is positive for carcinoma and the patient is a candidate for primary surgical treatment, radical axillary dissection is performed. If the BAAF is negative, the search for the sentinel lymph node should be performed when offering local surgical control. If the axilla is clinically and radiologically negative, a sentinel lymph node is performed. If sentinel lymph node is performed in conjunction with conservative surgery, the presence of 1-2 positive lymph nodes does not warrant completing the radical dissection of the axilla since local control will be consolidated later by radiotherapy. If a sentinel lymph node is performed in conjunction with a total mastectomy and it is positive in the trans-operative study, the radical axillary dissection should be completed.
- Patients with positive hormone receptors should always receive anti-hormonal treatment as part of their adjuvant management. They must also receive chemotherapy according to:
- Age equal to or less than 35 years.
- Tumor grade (high).
- Presence of lymphovascular infiltration.
- Tumor size ≥ 2 cm.
- Positive lymph nodes.
- High Oncotype Recurrence Score (> 25 in women > 50 years, score from 16 to 25 in women < 50).
- Patients with hormone-sensitive tumors considered candidates for chemotherapy should receive hormone therapy after completion of chemotherapy.
- Patients with overexpression of HER2 neu should receive targeted anti-HER2 therapy in addition to systemic chemotherapy. If there is expression of estrogen and/or progesterone receptors, the patient will subsequently receive anti-hormonal treatment.
- Triple-negative patients should be offered adjuvant chemotherapy if tumor size is ≥ 0.5cm. This group of patients is not a candidate for hormone therapy.

Treatment in locally advanced disease

Patients with locally advanced breast cancer are usually offered systemic neoadjuvant treatment initially. The goal is to induce response before surgical treatment and improve operability or allow breast preservation if possible [60]. Neoadjuvant treatment also makes it possible to assess the response *in vivo*. In some cases, it may be decided to offer primary surgical treatment with subsequent adjuvant treatment, according to pathological variables. Disease-free survival and overall survival rates are comparable in patients receiving initial neoadjuvant therapy and those undergoing primary surgical treatment [60].

After neoadjuvant treatment, the surgical treatment modality is selected according to initial clinical variables and response (conserving surgery vs. total mastectomy and sentinel lymph node vs. radical axillary dissection). Adjuvant radiotherapy is also offered according to clinical variables before and after neoadjuvant treatment. The possibility of immediate or delayed reconstruction should be considered according to the wishes of the patient.

Neoadjuvant chemotherapy regimens commonly administered are based on anthracyclines and taxanes or regimens without anthracyclines with taxanes and platinums. In triple negative tumors, schemes with carboplatin with anthracyclines and taxanes are usually offered [60].

Hormonal therapy or anti-hormonal treatment is administered for 5-10 years. The drug is chosen according to the hormonal status of the patient at the time of diagnosis. Some patients are considered

candidates for surgical castration and subsequent use of aromatase inhibitors.

Recommendation

- In most patients with positive hormone receptors, it is recommended to use neoadjuvant chemotherapy (greater response in less time), although in some cases neoadjuvant hormone therapy may be chosen.
- Neoadjuvant hormonal treatment is not recommended in pre-menopausal patients.
- In patients with neu HER2 overexpression, targeted treatment with trastuzumab ± pertuzumab + systemic chemotherapy is offered.
- In patients without over-expression of HER2 neu, third-generation schemes are offered (Table 6).
- In patients with triple negative tumors, neoadjuvant systemic chemotherapy is offered.
- In postmenopausal patients, aromatase inhibitors (letrozole, anastrozole, exemestane) and, in some cases, selective estrogen receptor modulators (tamoxifen) will usually be prescribed.
- In pre-menopausal patients treatment with tamoxifen or double hormonal blockade with goserelin + tamoxifen vs aromatase inhibitor is offered.

Epirubicin/cyclophosphamide, adriamycin/cyclophosphamide followed by weekly paclitaxel.
Adriamycin/cyclophosphamide followed by docetaxel three weeks.
Docetaxel/adriamycin/cyclophosphamide.
Docetaxel/cyclophosphamide.
Dose dense adriamycin/cyclophosphamide, followed by dose dense paclitaxel.
Dose dense adriamycin/cyclophosphamide, followed by weekly paclitaxel.

Table 6: Chemotherapy schemes in patients without overexpression of HER2 neu.

Treatment in patients with metastatic disease

In this group of patients, treatment is palliative. The selection of systemic treatment is made based on biological variables, symptomatology, and sites of metastatic disease.

Effect on fertility according to treatment by clinical stage

The effect on the fertility of patients with breast cancer depends on the treatment modality implemented. Standard treatments for breast cancer can have a negative impact on reproductive health, either directly by causing ovarian failure or by delaying pregnancy-seeking associated with treatment.

Radiotherapy

The amount of radiation that reaches the ovaries and uterus by scatter during treatment directed at the breast and axilla is relatively low, so the gonadotoxic effect should be minimal.

Recommendation

- The use of barriers is recommended to protect the pelvic area.
- Pregnancy should be postponed until radiotherapy is completed.

Systemic treatment/chemotherapy

Alkylating agents (cyclophosphamide) have the highest rate of gonadotoxicity, with amenorrhea in 40-60% of women who receive them before the age of 40 years and in more than 80% of women older than 40 years [61].

Anthracyclines are less gonadotoxic than alkylating agents; however, they are also associated with high rates of amenorrhea [61].

Taxanes are associated with amenorrhea when used in conjunction with anthracyclines and cyclophosphamide.

The effect of anti-HER2 targeted therapies on fertility is rather associated with the concomitant use of chemotherapy. Trastuzumab treatment, by itself, does not contribute to amenorrhea [61].

Recommendation

It is recommended not to try to get pregnant for at least 7 months after completing anti-HER2 treatment due to the risk of teratogenicity.

Endocrine treatment

The greatest impact that the use of anti-hormonal treatment has on the fertility of patients is the resulting delay in seeking conception. Concerns regarding the impact of tamoxifen on fertility in those who desire pregnancy have been associated with nonadherence to treatment. In addition, tamoxifen has shown teratogenic effects [62].

The POSITIVE study [60] seeks to establish the safety of pregnancy in women with hormone-sensitive breast cancer who are administered hormone therapy for 18-30 months with a rest period of three months before conception. A two-year window is offered to allow for pregnancy and lactation. After these two years, the restart of hormone therapy is contemplated to complete 5-10 years of treatment.

Recommendation

In patients with hormone-sensitive tumors, the use of tamoxifen is recommended, with or without ovarian suppression, or the use of aromatase inhibitors associated with ovarian suppression, for 5 to 10 years, depending on the clinical stage at the time of diagnosis and the ganglion state.

Measures to preserve fertility according to the clinical stage

All women of reproductive age diagnosed with breast cancer and who are interested in preserving their fertility should be referred in a timely manner to fertility specialists.

Low ovarian reserve and older age open the door to having a realistic and objective discussion with the patient about the chances of success in capturing her own oocytes and the possibility of pregnancy with them. The specialist indicated for this discussion with the patient is the Reproductive Biologist.

Recommendation

- It is recommended to carry out a baseline fertility evaluation measuring Anti-Müllerian Hormone (AMH), Follicle Stimulating Hormone (FSH) and Estradiol (E2) in the early follicular phase, as well as Antral follicle count by vaginal ultrasound.
- It is recommended to talk about highly complex Assisted Reproduction techniques such as *In Vitro* Fertilization (IVF), egg donation, surrogate uterus and adoption.

Cryopreservation of oocytes or embryos

Oocyte or embryo cryopreservation is the best established therapy with the highest success rate for patients with sufficient ovarian reserve and for those who are medically stable to start controlled ovarian stimulation [62]. There are different types of stimulation protocols, as indicated by the reproductive biologist, designed to minimize the delay time to start or continue a specific cancer treatment; for example, the "random start" protocols that may require one or two weeks and start at any time of the cycle and can even be carried out several cycles before or after breast surgery to achieve an optimal number of oocytes. Patients subjected to this treatment have shown no difference in recurrence and survival [63]. There is no difference in the time at the start of the next therapeutic modality.

The options of cryopreserving mature oocytes or embryos have shown equivalence in success to achieve pregnancy [61].

Recommendation

Concomitant treatment with aromatase inhibitors to minimize elevation of estrogen levels may be indicated in some cases, without compromising results.

Pre-implantation genetic diagnosis for mutations (PGT-M) is suggested for patients with known mutations.

Other alternatives

Concomitant use of Gonadotropin Releasing Hormone (GnRH) agonists.

The administration of GnRH agonists, goserelin or leuprolide, concomitantly with chemotherapy, decreases the rate of ovarian failure. A meta-analysis of 5 trials showed a decrease in the rate of premature ovarian failure (14.1 vs 30.9) [64].

Recommendation

It is recommended above all in patients considered non-candidates or who cannot access other proven preservation methods, such as cryopreservation.

Preservation of ovarian tissue

It involves the surgical excision of ovarian tissue by laparoscopy with unilateral or bilateral oophorectomy. Tissue strips are prepared and cryo-preserved for thawing and later use. There is

a hypothetical risk of malignant cell seeding and the possibility of second primaries in BRCA mutation carriers in the autologous transplant scenario.

Recommendation

It is recommended in patients who cannot receive controlled ovarian stimulation due to oncological indications, in patients who immediately decide on a fertility preservation technique, single women who want another alternative in conjunction with controlled ovarian stimulation.

In vitro follicular maturation

The maturation of immature oocytes is no longer an experimental technique at present. Oocytes can be obtained immature, given the rush to start cancer therapy, to be matured in the laboratory or cryo-preserved.

It is important to highlight that today, despite not being experimental, the maturation of immature oocytes is still not performed routinely in our country; however, it is highly recommended to consider an alternative option before or after cryopreservation. Hence, its widespread development and implementation is necessary in the near future.

Recommendation

Patients who are not allowed controlled ovarian stimulation for oncological indication, on any day of the patient's menstrual cycle. There is no time for controlled ovarian stimulation or cryopreservation of ovarian tissue.

Use of hydrogels with encapsulated follicles.

It consists of the transplantation of immature follicles encapsulated in hydrogels to the patient with subsequent maturation *in vivo*. It has been successfully achieved in murine models.

Recommendation

Consider as a possible option for patients in the premenarche and for those not candidates for ovarian stimulation who have cryopreserved ovarian tissue.

Pre-implantation genetic diagnosis (PGT)

Young patients diagnosed with breast cancer should be seen by specialists to rule out hereditary cancer syndromes associated with genetic mutations. The identification of mutations has implications not only for treatment selection and surveillance, but also for fertility.

Recommendation

In young patients with breast cancer, pre-implantation genetic diagnosis for aneuploidies (PGT-A) is suggested, which could allow the selection of an embryo that does not carry the mutation. In patients with positive BRCA1.

Cancer in girls and adolescents

The overall prognosis for children and adolescents with cancer has improved greatly in the last half century. In the mid-1970s, 58% of children (ages 0 to 14 years) and 68% of adolescents (ages 15 to 19 years) diagnosed with cancer survived at least 5 years. From 2008 - 2014, 83.4% of children and 84.6% of adolescents diagnosed with cancer survived at least 5 years [65,66].

In Mexico, the National Childhood Cancer Program (2017) of the Seguro Popular (Secretary of Health), the Pan American Health Organization (PAHO) and the Global Cancer Control (UICC) reported childhood cancer as the main cause of death among children. 5 and 14 years. The incidence is 5,000-6,000 cases per year, of which 65% are diagnosed in advanced stages of the disease. Overall survival at 5 years is less than 40%, representing more than 2,300 lives per year [67].

Types

The main neoplasms observed in girls and adolescents are: leukemia (50%), lymphomas, tumors of the Central Nervous System, germ cell tumors, soft tissue sarcomas, renal bone sarcomas, retinoblastoma, neuroblastoma, liver, carcinomas and melanoma [67].

Treatment

Treatments must be carried out with multidisciplinary teams, since they will require surgery, chemotherapy and radiotherapy according to the type of tumor and clinical stage.

Infertility risk factors

The effects on fertility of gonadotoxic treatments depend on various factors:

- Factors related to the patient: Age and sex.
- Factors related to treatment: Type of drug used, dose, cumulative dose of chemotherapy, place of radiation and type of surgery performed [68].

The anti-neoplastic agents reported with the highest toxicity at the level of the gonad are the alkylating agents [69,70].

Risk factors for infertility in girls

In girls, risk factors for infertility include:

- Age: The closer the reproductive age is to cancer treatment, the greater the risk of subsequent infertility.
- Cumulative dose of alkylating agents (particularly cyclophosphamide, lomustine and procarbazine) and
- Diagnosis of Hodgkin's lymphoma [68,71].

Effects on fertility according to treatments

Pediatric fertility preservation is an emerging and evolving field [68] that requires a multidisciplinary evaluation of the case, including oncologists, reproductive biologists, pediatric psychologists and, of course, parents or guardians with the patient.

Infertility rates in female childhood cancer survivors in the literature range from 16-41% [68,72,73].

Recommendation

The information to be offered in a complete, updated, accurate and timely objective manner must be offered by the gynecologist specializing in reproductive biology and the oncologist together.

Radiotherapy

Abdominal and/or pelvic radiation can damage the female reproductive organs. Higher doses of radiation to the ovaries, especially above 10 Gray, increase the likelihood of acute ovarian failure or premature nonsurgical menopause [68].

Ovarian/uterine radiation doses greater than 5 Gray decrease the probability of pregnancy [68].

Radiation to the Central Nervous System (CNS, hypothalamus/pituitary) can cause hypogonadism [68].

Surgery

Oophorectomy conditions different fertility disorders to different degrees [70,74,75].

Measures to preserve fertility

Cryo-preservation

The most common fertility preservation options in the peri-pubertal and post-pubertal stages include cryo-preservation of oocytes, embryos or sperm in the case of boys [7,68], although cryo-preservation of ovarian tissue and spermatids in those prepubertal patients.

Recommendation

Cryo-preservation of oocytes and/or ovarian tissue should be offered and valued jointly with the patient's family. This orientation should always include a reproductive biologist.

Before initiating chemotherapy, radiotherapy or surgery, timely and adequate counseling should be provided to the parents -and to the patient, when indicated- from the point of view of reproductive biology [68].

Women of childbearing age with non-gynecologic cancer

According to the Globocan report [2] and, excluding gynecological tumors, the most frequent tumors in fertile age in Mexico (Figures 3 and 4) are:

- Thyroid (50% present in < 40 years).
- Liver and biliary tract (only 2% in women < 40 years).
- Colon and rectum (only 8% in < 40 years).
- Stomach (< 5% in < 45 years).
- Leukemias and Lymphomas (especially in adolescents).

Treatment according to type of cancer

Liver and stomach cancer

Assuming the high mortality of liver and stomach tumors, we believe that the issue of fertility in these tumors is of little relevance.

Thyroid cancer

In thyroid cancer, the primary treatment is surgery and, in some cases, supplemental radioactive iodine [76].

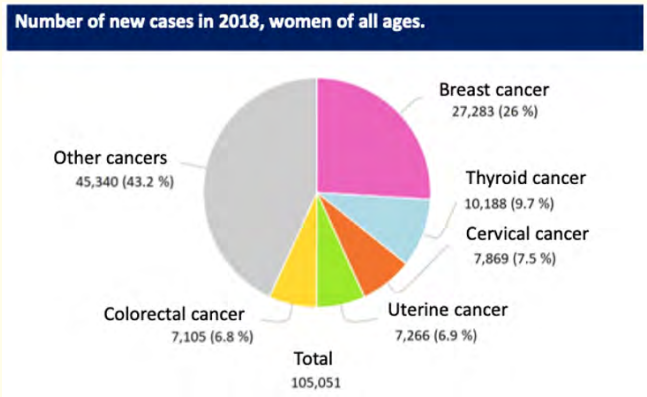

Figure 3: Number of new cases in 2018 of cancers in women of all ages [2].

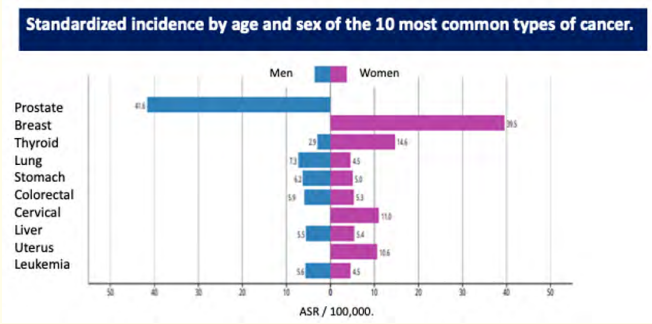

Figure 4: Standardized incidence of the 10 most common types of cancer, by sex and age [2].

The impact that a dose of iodine might have on fertility is unknown; however, and when in doubt, it is considered important and good clinical practice to refer women with a desire for fertility for evaluation by a reproductive biologist.

Recommendation

Refer women with thyroid cancer and a desire for fertility for evaluation by a reproductive biologist.

Colon cancer

The primary treatment for colon cancer is surgery [77].

Only in cases where chemotherapy is necessary, referral to specialized centers should be considered where the reproductive biologist, together with the rest of the multidisciplinary team, adequately, objectively and timely orients the patient on the preservation of her potential reproductive in the future.

Recommendation

Refer the patient with colon cancer to specialized reproductive centers when the patient must be treated with chemotherapy, with the aim of guiding on the preservation of her reproductive potential in the future.

Hematological cancer (Leukemias and lymphomas)

Leukemias and lymphomas are the province of the hematologist and the treatment includes high doses of chemotherapy [78,79]. For this reason, in patients considered curable, they should be oriented on the possibility of fertility preservation by a group of experts that includes a reproductive biologist.

Recommendation

Patients with hematologic cancer that are considered curable should be counseled on the possibility of fertility preservation by a group of experts that includes a reproductive biologist.

Effect on fertility according to treatment

The chemotherapy schemes used are multiple and with different toxicity profiles. The effect on fertility of many cancer drugs is unknown.

Recommendation

A multidisciplinary evaluation including a reproductive biologist should be considered for all women with cancer who desire fertility.

Measures to preserve fertility according to stages.

Recommendation

- It is considered essential to have multidisciplinary teams for the best approach to patients.
- They should always be referred to specialized centers for their approach and the urgency, or not, of starting chemotherapy should be precisely established.
- The team of experts will decide, together with the patient and her family, the best available method (cryo-preservation of ovarian tissue, oocytes or embryos, etc.) to preserve her future fertility.

Fertility in men

Given that germ cell (testicular) tumors, lymphomas, and leukemias are very common in young men [80), a special section for this item will be included in subsequent consensuses; however, if it occurs, the patient and his family must be provided with the possibility of preserving future fertility. This should be discussed with a multidisciplinary team including a reproductive biologist.

Recommendation

Provide the patient and her family with the possibility of preserving future fertility.

Technical aspects: controlled ovarian hyperstimulation

Time is a very important factor for all infertility patients: the older you are, the lower the quality and quantity of oocytes. It is crucial for those who have oncological diseases where, in addition to the disease, time is added, generally short, to be able to start the medical or surgical management of their oncological process.

In the assessment of a cancer patient with an indication for fertility preservation, there must be perfect synchronization between the Reproductive Biologist and the treating Oncologist to share the diagnosis, medical and/or surgical management to be carried out and their prognosis. The type of medication or radiation and the dose used will give us an idea of the damage that your ovarian reserve may suffer. The moment in which the treatment will begin is fundamental, since the type of preservation that will be carried out will depend on it [3].

Schemes for Controlled Ovarian Hyperstimulation (COH) in the same cycle, or maximum one cycle later.

Preservation of extreme urgency

It is considered of extreme urgency when the start of the treatment will be immediately or before the next 10 days.

In these cases, it is impossible to carry out a controlled ovarian hyperstimulation protocol, so the only alternatives available to preserve oocytes are *in vitro* maturation or ovarian tissue freezing.

Likewise, administration of a gonadotropin-releasing hormone depot analog can be tried to provide pharmacological protection of the ovaries. Although there are controversial results regarding its use, it is known that there is no greater harm and it may offer advantages in some patients [61].

In vitro maturation of oocytes

It is a highly complex technique that few centers in the country can perform. Adequate training is required, both of the Reproductive Biologist for the aspiration of the follicles and of the Embryologist for their identification and correct handling [81].

In vitro oocyte maturation requires the aspiration of follicles to obtain immature oocytes, mature them in the reproduction laboratory and subsequently freeze them. Although it is ideal to perform it during the early follicular phase, this technique can be performed on any day of the cycle. There are articles that find no difference between doing it in the follicular or luteal phase.

Although not essential, follicle-stimulating hormone (FSH) can be added three days prior to promoting follicular growth.

A dose of 10,000 IU of Human Chorionic Gonadotropin Hormone can also be added 38 hours before aspiration to favor the restart of oocyte meiosis and accelerate their maturation process. The addition of Human Chorionic Gonadotrophin Hormone to *in vitro* maturation modifies the terminology of the procedure and today it would be called *in vivo* maturation [81].

The number of oocytes obtained is variable depending on the ovarian reserve.

Recommendation

- The oocyte maturation technique must be performed in highly specialized centers.
- Although it can be done on any day of the cycle, it is recommended to do it during the early follicular phase.
- You can consider adding FSH three days before aspiration and/or 10,000 IU of Human Chorionic Gonadotropin Hormone 38 hours before.

Ovarian tissue freezing

It is a technique considered experimental, although more than 130 live births have already been obtained throughout the world, including in pre-pubertal patients [62].

It can be done at any time through laparoscopy and removing from a fragment to the entirety of one of the ovaries, it is never recommended to remove both. Once the ovarian tissue has been removed, it is processed in the laboratory by dissecting the ovarian cortex tissue (approximately 3mm) and removing the stromal tissue. They are cut into small pieces and frozen, either by a slow technique with a programmable freezer or by vitrification [3]. The recovery of the patient is very fast and there are very few complications inherent to the technique.

The advantage is that, when the ovary is transplanted, the recovery rate of its function is very high, greater than 90%, with which it is possible to have a not very limited number of oocytes, which is what happens when freezing exclusively oocytes. In addition, the ovarian tissue can also be preserved during the course of some abdominal surgery, taking advantage of that surgical time for the removal of the ovarian tissue [62].

As a disadvantage, it stands out that it is an invasive procedure that requires a surgical intervention, even if it is ambulatory [62].

For the freezing of ovarian tissue, a mixed preservation technique can be performed. It consists of aspirating the follicles that can be seen with the naked eye or through a stereoscopic microscope before freezing the ovary cortex. Aspiration is done with a 21G needle. The aspirated fluid is checked immediately to observe the presence of oocytes, generally they will be immature, except when the surgery is performed very close to the day of ovulation, in which case a mature oocyte can be recovered. After identification, they mature for 24 to 48 hours, vitrifying the mature oocytes obtained [3].

Recommendation

- The freezing of ovarian tissue and/or *in vitro* maturation of oocytes will be used in the event that there is a contraindication to perform ovarian stimulation or that the start of oncological treatment is imminent.
- Both ovaries should never be removed.

Emergency Preservation (in the same cycle or maximum one cycle later)

- Controlled ovarian stimulation.
- When we have more days to start cancer treatment, there is the possibility of performing controlled ovarian stimulation.
- In the past, stimulation was initiated in the early follicular phase and later in the luteal phase with similar results [82].
- Today it is known that follicles are recruited in up to three waves within an ovarian cycle [83]. This extremely dynamic follicular development allows follicular development to be stimulated at various stages of the cycle and allows us to start stimulation from the day the patient arrives [63]. This protocol, called random start, has provided flexibility in starting COH and optimizes the days we have to perform fertility preservation [84].

Controlled ovarian stimulation technique

Ovarian stimulation is performed with recombinant follicle-stimulating hormone or with menotropins in variable doses of 150-300 IU daily, depending on the ovarian reserve of follicles, with ultrasound monitoring. From the start of ovarian stimulation, 5 mg daily, orally, of an aromatase inhibitor (Letrozole) or 60 mg daily of tamoxifen are added to block the conversion of androgens to estrogens and prevent their significant increase [40].

When at least two follicles reach 14 mm, a daily dose of GnRH antagonist (cetrotide 0.25 mg) is added until reaching a diameter close to 18 mm in the dominant follicles. For the final induction of oocyte maturation, 0.2 mg of triptorelin acetate (gonapeptyldaily) is used. Gonadotropin-releasing hormone analog (triptorelin) is preferred for maturation instead of human Chorionic Gonadotropin Hormone because it raises estradiol levels less. After 37 h, follicular aspiration was performed by transvaginal puncture guided by transvaginal ultrasound. The aromatase inhibitor is continued until the patient's menstruation [40].

A second ovarian stimulation can be started 4 days after follicular aspiration. In this case, we continue the aromatase inhibitor and the stimulation is repeated as previously described. This double stimulation is another advantage of follicular recruitment in waves. This protocol is called "Duo Stim" or double stimulation in the same cycle [85]. The quantity and quality of oocytes are similar to those of the first stimulation. This Duo Stim protocol should be performed when the number of extracted oocytes is not sufficient to give the patient a good chance of pregnancy once she is cured of her oncological process. In this case, the aromatase inhibitor continues the entire cycle [86].

Recommendation

- It is recommended to use the random start protocol.
- For maturation, the use of a GnRH analog (triptorelin) is recommended instead of the Human Chorionic Gonadotropin Hormone.
- When the number of extracted oocytes is not sufficient, the use of the "DuoStim" protocol is recommended.

Schemes for ovarian stimulation when two or more cycles are available

It has been found that, in general, from diagnosis to start of treatment, 90 days can elapse without the patient's prognosis being affected [3].

The number of oocytes needed should be assessed so that the patient has a good chance of having children later. The amount is directly proportional to age and this is why, when we have enough time, we can do the necessary number of stimulations until reaching the ideal number of oocytes.

Controlled ovarian hyperstimulation is carried out in the same way as mentioned above, with daily administration of aromatase inhibitors for the necessary cycles until the desired number of oocytes is achieved. The DuoStim technique and the start of stimulation on any day of the cycle (randomstart) can be used with the same considerations and ovarian tissue freezing and/or *in vitro* maturation if there is a contraindication to performing controlled ovarian hyperstimulation.

Recommendation

- It is recommended to assess the number of oocytes needed.
- You can use the DuoStim and RandomStart techniques.

Ethical aspects

Ethical aspects are very important in the preservation of fertility and must be present in various parts of the process.

The oncologist should inform his patients that fertility preservation can be performed and ideally give them an information document that the patient should sign. The oncologist should know that the start of cancer treatment can wait a few days, up to 90, without harming the patient's progress [3].

The reproductive biologist who assesses the patient must have complete knowledge of the cases that she is going to perform and be in direct communication with the responsible oncologist. Informed consent must be given to patients that perfectly explains the possibilities of performing the preservation and the possibilities of pregnancy once the preservation has been performed.

The clinics that carry out the preservation procedures must have a very clear knowledge of the techniques used to preserve fertility in order to offer them [87].

Recommendation

- The oncologist must inform the patient and obtain the information document signed by the patient.
- The biologist must collaborate closely with the oncologist. She must obtain the informed consent of the patient about the techniques to be performed and the possible results.

Legal aspects

The recommendations in the legal field are based on the results of the topics developed in this consensus on the preservation of fertility in women in Mexico.

General legal recommendations

- It is recommended that the oncologist make a referral to an expert in fertility preservation in those women who have a high chance of surviving cancer.
- There must always be informed consent for all patients (including minors).
- There must be commitment from the group of experts in fertility preservation, which is explicit and multidisciplinary.
- In patients under 18 years of age, the consent must be filled out through the custody of the parents; however, from the age of 16, through emancipation, women must be given the right to make their own decisions, with their consent.
- As long as embryos are frozen, the signature of the spouse is an essential requirement, although it is advisable to avoid the cryopreservation of embryos in order to reduce ethical, moral, political, social and economic problems, as well as embryos stored without future destination, especially in cancer patients.

- The patient or couple must decide the future fate of their gametes or embryos before starting a fertility preservation treatment, in case of death or separation, to avoid storing embryos without a specific purpose.
- You must have all the current tools (with scientific and experimental evidence) to offer the patient according to each case.
- It is understood as those with scientific evidence, those that have more than 100 pregnancies reported in their results (oocyte vitrification, *in vitro* maturation, preservation surgery such as oophoropexy and hysteropexy, gonad-protective treatments with gonadotropin-releasing hormone analogs.
- It is understood as those experimental, those that are in the period of study and that, although they do not have more than 100 pregnancies reported, offer considerable options in the future, such as vitrification of ovarian tissue.
- Current protocols in ovarian stimulation should be used and individualized: Duo-Stim (double stimulation in the same cycle), random start (Random stimulation), in addition to using as a strategy in patients with hormone-dependent cancer (breast or endometrial), inhibitors of aromatase (letrozole) and anti-estrogens (Tamoxifen), to avoid the excessive peak of estradiol; taking into account that gonadotropin-releasing hormone analogs should always be shot to improve oocyte quality (cytoplasmic and nuclear maturation) and suppress the luteal phase.
- It is recommended that the oncologist give consent to start reproductive treatment, when the patient is in a disease-free period.

Legal recommendations on cryopreservation

- It is always recommended to vitrify using an open utensil to obtain a 100% survival rate.
- It is recommended to cryopreserve at least 8 to 10 oocytes, depending on age and ovarian reserve, to have a good chance of future pregnancy; The reproduction center is committed to having a high rate of progression to blastocyst and having strict quality controls in the laboratory.
- To cryo-preserve ovarian tissue, vitrification is widely recommended instead of slow phase, since the current international literature reports better rates of tissue longevity after orthotopic or heterotopic transplantation.

Other legal recommendations

- In those women who defer maternity (by social reason), they should be advised not to seek pregnancy after 50 years of age, given the increased incidence of hypertensive disorders in pregnancy, gestational diabetes and intrauterine growth retardation , among others.
- According to the sexual conceptualization in fertility preservation in same-sex couples and in the process of performing transgender surgery, it will be recommended to cryo-preserve oocytes and/or ovarian tissue, before receiving hormonal treatment, which can damage the gonad; It is important that the consent be signed with the final identity card, once the surgery has been performed.

Non-oncological preservation: Social and different sexual Conceptualization. Indications and contraindications

Non-oncological medical indications to preserve gametes and/or gonadal tissue [88].

- Patients with non-oncological diseases that require:
- Gonadal extirpative surgery (endometriosis, benign cystic teratomas),
- Chemotherapy or radiotherapy:
- Autoimmune diseases (refractory to other treatments: SLE, RA, scleroderma, etc.)
- Hematological diseases (sickle cell anemia, thalassemias, aplastic anemia, etc.)
- Patients requiring chemotherapy for bone marrow transplantation.
- Patients requiring bilateral oophorectomy for severe endometriomas or benign ovarian tumors.
- Imminence of premature ovarian insufficiency.
- Genetics (with or without family history) or
- Acquired (due to planned surgeries, exposure to environmental agents, decreased ovarian reserve not consistent with age).
- Before definitive sterilizations. Inform patients of preservation options. There will be groups with a higher risk of requiring due to age, low ovarian reserve and high risk of decision changes.

Non-medical or social indications to preserve gametes and/or gonadal tissue.

- Postponing pregnancies for more advanced ages.

This is an increasingly widespread trend and is currently the most common cause of fertility preservation. In this case, it would be recommended that the preservation be carried out in those under 35 years of age, although it can be applied to ages up to 38-40. In this last group, it is highly recommended to carry out preimplantation genetic testing. Recommend trying natural conceptions at an earlier age, not giving the false hope that it is insurance against later infertility and emphasizing that it will require assisted reproduction and that the use of vitrified oocytes is not ruled out because pregnancy is achieved with spontaneous conception or because she does not want to be a single mother or use gametes from a donor.

Inability of the couple to attend an assisted reproduction procedure.

Special groups. Preventive in women with mutations at high risk of neoplasms that require bilateral salpingo-oophorectomy.

Recommendations

- The preservation of gametes and/or gonadal tissue should ideally be performed in patients under 35 years of age.
- It is recommended to carry out preimplantation genetic testing if it is performed in women aged 38-40 years.

Absolute or relative contraindications (due to risk for them or for newborns).

Contraindications for ovarian stimulation [89]

- High risk that ovarian stimulation causes life-threatening conditions (systemic pathology, congenital cardiovascular anomalies, etc.
- Patients who do not have time or conditions for it.
- Elderly patients with low ovarian reserve and increased risk of chromosomal abnormalities.

Contraindications for embryo transfer [90]

- High risk of a pregnancy causing life-threatening complications.
- Physical or mental inability to care for a newborn.
- High risk of diseases in the newborn, if they have not been ruled out with PGD.

Fertility preservation in women with different sexual conceptualization.

Most international scientific organizations emphasize not discriminating against people in their desire for fertility based on their sexual orientation and the well-being of children raised by same-sex couples.

Indications

- **Lesbian patients:** The indications to preserve their fertility are similar to women with a different sexual orientation. They will require donor sperm and psychological evaluation.
- Transgender patients.

Recommendation

- If they are going to receive androgens for masculinization, the ideal would be to vitrify oocytes before receiving hormonal therapy.
- More intensive psychological evaluation should be performed when hysterectomy is desired.

Contraindications

Contraindications are the same as for other types of fertility preservation.

Information they should receive before presenting age-related ovarian insufficiency

- All these procedures will require subsequent assisted reproduction.
- The real chances of success in your particular case.
- Which procedures are in the experimental stage.
- The prognosis of each technique, particularly in its specific case.
- The recommended number of oocytes to have the opportunity to transfer a euploid blastocyst, since as age advances, the probability of euploidy in blastocysts decreases and the

number of oocytes that need to be preserved increases. Today, fairly accurate mathematical calculations are available to establish this number and forecast.

- The need for PGD in special cases.

Non-oncological preservation: ethical aspects

The principles that should be applied to the preservation of fertility in non-cancer patients are:

- **Charity:** It would be in this area the preservation of Fertility.
- **No Maleficence:** Try to reduce stress through the measures required to preserve fertility.
- **Justice:** Fertility preservation options should be offered to all.
- **Autonomy:** Patients must actively participate in making a free and informed decision to preserve fertility.

Cryopreservation

The cryopreservation of mature oocytes offers a result similar to that of cryopreserved embryos [91], so today embryo cryopreservation can be avoided. Heterotopically placed cryopreserved ovarian tissue demonstrates success in preserving primordial follicles [92].

Without a doubt, this practice has ethical and legal implications that address issues such as *in vitro* maturation, religious conflicts, children's rights, posthumous use.

Recommendations

In the case of non-oncological patients, such as rheumatic pathologies, immune or autoimmune suppression, gender and sex diversity, and gender dysphoria, these are indications that should be taken into account in order to include these procedures in those cases.

Cryopreservation of oocytes for non-medical reasons.

Recommendations

- The optimal age to vitrify oocytes should be between 24 and 34 years.
- The optimal number of oocytes to be frozen should be between 8 and 10.
- Security must be offered in the programs.
- The use of accumulated oocytes should be taken into account and promoted, previously analyzing the cost benefit and the ethical and social implications.

Preservation of fertility for social reasons

For good medical practice, indications, results and future perspectives of fertility preservation techniques must be taken into account [93].

Non-oncological indications include autoimmune diseases, cases of stem cell transplantation, premature ovarian failure, genetic disorders, sex reassignment procedures, delayed fertility [93].

The results indicate a rate of 22 to 50% of live newborns with cryopreserved oocytes and embryos and 62% with cryopreserved semen [93].

Recommendations

- The preservation of fertility should be considered a multidisciplinary decision.
- A local referral center should be located.
- You must refer the patient who wishes to preserve fertility to the specialist.

Preservation of fertility by different sexual conceptualization.

Gender and sex diversity and gender dysphoria are indications that should be taken into account in order to include fertility preservation procedures.

Recommendation

For transgender people, gametes should be preserved BEFORE considering identity-affirming therapy, gonadectomy, hormone treatment, or male and female transgender reproductive options.

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