Preserving Fertility in Ovarian Cancer

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In the last decades, by improving the oncological treatment, the life expectancy of the adolescent patients with ovarian cancer has been increased and more than that they have succeeded by a real chance of obtaining a future pregnancy. Thus, the problem of preserving fertility becomes paramount both for patients who have suffered from an oncological disease and for those up to the age of 40 who have fertility problems.

Keywords: oncological treatment, ovarian cancer, fertility conservation, future pregnancy

Unfortunately, due to the complexity of folliculogenesis (the presence in the ovaries of many follicles in different evolutionary stages), the conservation of female gametes is much more difficult than the male one. [1].

The mature oocyte is large in size but has a high concentration of water, which makes it very fragile and difficult to conserve [2].

The ovociteral administration depends on the age of the patient, the number of ovarian follicles and not least the gonadotoxicity of the adjuvant treatment needed. The upper limit of unanimously accepted age is 40 years [3].

The most commonly used chemotherapy regimens in ovarian neoplasm have been shown to have an average risk of gonadotoxicity: Doxorubicin, Carboplatin and Cisplatin, but there are chemotherapy therapies with a high risk of gonadal impairment, for example: Chlorambucil, Cyclophosphamide, Busulfan, etc. Pelvic radiotherapy can cause premature ovarian failure, uterine toxicity (through myometrial and endometrial atrophy, uterine hypoperfusion) [4,5].

Although the most common indications for preserving fertility are oncological conditions, and non-oncological ones may require this, such as: recurrent dermoid findings, recurrent ovarian endometriomas, genetic or idiopathic ovarian failure [6].

The main techniques of fertility conservation are:

A. Ovarian or embryonic preservation following ovarian stimulation

In order to be able to perform ovarian hyperstimulation, these patients must necessarily have no contraindication for this (although, very high levels of estradiol during the stimulation period are not beneficial, so the most common ovarian stimulation with aromatase inhibitors is recommended: Letrozole) and may also be allowed to delay the initiation of chemotherapy treatment by about 2 weeks. Ovarian stimulation cannot be performed in an emergency and it cannot begin if chemotherapy has already been started. However, it seems that hyperstimulation performance is lower than in infertile patients [7].

B. Ovarian or embryonic preservation without ovarian stimulation

In fact, it represents the collection of oocytes in various evolutionary stages and their maturation in vitro. The cumulus-oocyte cultures are incubated for about 48 hours and only those that become mature will be vitrified. Unfortunately, it seems that, according to statistics, only 50% of the oocytes will be able to mature [8].

Oocyte preservation involves a special, highly sensitive procedure of intracytoplasmic sperm injection into the oocyte cell (ICSI), with a fertilization rate of about 60%. Embryos can be frozen on day 2 or 5 (blastocyst). Survival rate after 90% cryopreservation. They are transferred intrauterine after a prior hormonal preparation of the endometrium (suitable for implantation)

Oocyte conservation, extremely difficult to achieve until recently, has reached a survival rate after thawing of about 80%. Moreover, it has been found that these oocytes have relatively equal chances of fertilization with fresh ones [9].

In addition to the classical technique of transvaginal ultrasound-guided follicular puncture, there are surgical techniques for preserving fertility.

Ovarian tissue preservation is still an experimental variant and involves laparoscopic ovarian cortex harvesting. The primordial and primary follicles will be frozen slowly and then after thawing they will be re-implanted in the pelvic cavity. So far, it has been possible to obtain about 40 tasks in the world through this technique [10].

The main purpose of the ovarian transposition is to preserve the pelvic pre-irradiation function by ovarian transposition outside the hemipelvis, at least 3 cm away from the irradiation field. Its local limit is marked by placing a metal clip. Unfortunately, it has been found that the quality of the oocytes is affected most of the time and that the uterine tubes left in place have a risk of infarction, so that an assisted human reproduction technique can be used in the end [11].

There are in fact 4 variants of surgical approach: cryopreservation of the ovarian testis, oocyte sampling, ovarian transposition and ovarian tissue self-transplantation. Following the data collection of about 2000 specialized studies, the following results were found: most patients underwent ovarian tissue cryopreservation, followed by oocyte sampling, ovarian transposition and ovarian tissue self-transplantation. However, statistical data on the evolution of these patients are limited, so the conclusions could not be drawn [12].

The main argument for which the weight of ovarian tissue cryopreservation is the majority is the short time, effectively elapsed from the moment of diagnosis to the procedure itself. In a Danish study, published in 2019, in which the vast majority of patients opted for cryopreservation of ovarian tissue, it was found that the average of this time was about 6 days; obviously a much shorter time than the preservation of oocytes, which

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requires ovarian stimulation in order to obtain a reasonable number of oocytes (the ovarian stimulation protocols in these cases remain extremely controversial)[13].

Cryopreservation of ovarian tissue with peritoneal re-implantation at the end of neoadjuvant treatment may be unfortunately still considered experimental by many infertility specialists and taking oocytes before initiating chemotherapy may prolong treatment initiation and this is often not possible [14].

In a study conducted between 2011 and 2017 in which ovarian tissue sampling was performed in 64 patients with ovarian neoplasm, of whom about half were in premenarche and it was established that they had a risk of over 80% to develop ovarian failure prematurely after chemotherapy treatment, it was found that the intervention was easy, without complications and especially without delaying the initiation of the specialized treatment [15].

In the case of Borderline ovarian tumors in patients with a desire for procreation, two types of conservative surgery can be chosen: unilateral ovarectomy or classic or laparoscopic unilateral ovarian cystectomy, with systematic preservation of the uterus and possibly biopsy of the control ovary. According to studies it has been observed that the choice of the interventional type does not influence the rate of disease recurrence, but it can affect the subsequent fertility of the patients (assuming that the surgical maneuver on an ovary is more complex as its reserve may decrease)[16].

Although the current tendency is to perform conservative surgery in order to preserve patients' fertility, the histo-pathological type and degree of tumor differentiation dictate the possibility, so that only epithelial tumors of serous / mucinous origin, non-epithelial and with increased degree of differentiation may be candidates for this type of surgery [17].

Unfortunately there are cases with early onset of the disease, even prepubertarian. Due to the oncological treatments followed, the function of the hypothalamo-pituitary-gonadal axis can be significantly altered. The modalities by which a chance of prosecution can be given to these patients are limited and can only be implemented after a careful selection of cases [18].

In front of a young patient with incipient ovarian neoplasm, with reduced malignant potential (Stage IA) or non-epithelial ovarian tumor, conservative surgery may be considered, in order to preserve fertility.

If it is decided to perform a unilateral anexectomy, the surgical exploration for the purpose of correct staging must be extremely thorough. Multiple biopsies are recommended from the omentum, appendix, pelvic lymph nodes and paraAo and at the level of the contralateral ovary. All biopsies must be negative. It is also necessary to palpate all peritoneal surfaces, biopsy all suspicious formations and biopsy uterine cleansing to exclude endometrial neoplasm.

In front of a normal macroscopic controlateral ovary, it is not mandatory to biopsy it because the statistical data show that the incidence of a bilateral ovarian neoplasm at the time of staging an incipient disease is reduced, about 2.5%. Moreover, any surgical approach to a healthy ovary can decrease its fertility.

On the other hand, patients who opt for conservative surgery should be informed that there is limited data regarding the frequency of relapses, the risks of surgery, subsequent hormonal contraception or the role of drug-induced ovulation [19].

Young women, who were operated conservatively for ovarian tumors well differentiated in stage IA, should also be informed about the recommendation of performing total hysterectomy with contralateral anexectomy, after the age of 35 years or earlier if preservation of fertility is no longer a goal [20-23].

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