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Review

Special issues in fertility preservation for gynecologic malignancies

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ABSTRACT

Gynecologic malignancies account for 1,09 million new cancer cases worldwide consisting of about 12% of tumors affecting female population. About 10% of all female cancer survivors are younger than 40 years of age. Since cancers affecting female genital organs are usually treated by radical surgery, chemotherapy or chemoradiation approaches that induce permanent damage of reproductive functions, the development of strategies for fertility preservation represent one of the most important goals for gynecologic oncology. In this scenario, the newly defined oncofertility discipline acquires increasing interest, offering patients maximal chances to make an adequate decision about future fertility, based on their oncologic diagnosis and prognosis. However, the majority of physicians do not pay particular attention to these issues, even if impressive progresses have been made in this field in the last decades. Possibly, it is due to the lack of strong evidences from clinical trials without an adequate number of cases to establish safety and efficacy of these procedures. In this review we will discuss the most recently debated options for fertility preservation in gynecologic oncology, highlighting issues and controversies related to oncofertility.

1. Introduction

1.1. Background

The median age at first delivery is constantly rising in developed countries due to the trend to postpone parenting for social reasons (Shufaro and Schenker, 2012). Between 2006 and 2010, the percentage of patients older than 40 years who had a first pregnancy was approximately 20% (Finer and Philbin, 2014). Thus, the inci-

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dence of cancer before completion of the reproductive pathway tends to be higher. According to GLOBOCAN series, 6.7 million of new cancer cases and 3.5 million of cancer deaths have been estimated worldwide among female populations in 2012 (Ferlay et al., 2015). Cancer Statistics reported that about 10% of cases of tumors affecting female population are patients younger than 40 years (Siegel et al., 2014). Different solid tumors show significant differences in distribution of pathologic factors between younger and older patients and reduced survival has been reported for younger ones. The reason why tumors that occur in younger women are characterized by a worse prognosis is still unclear. Probably, the age appears to be a surrogate for aggressiveness or different tumor biology and this would explain why tumors developed by young women tend to have poorer outcomes even if treated by conventional treatments. Nonetheless, many studies seem to indicate that young age is an independent prognostic factor, at least in some tumors, such as breast cancer (Partridge et al., 2014). However, "2014 Cancer Statistics" reported that during the last 5 years, cancer death rates has decreased by 1.4% per year in young women as well, probably due to a more precise and earlier diagnosis and more effective treatments (Siegel et al., 2014). Moreover, evidences showed that pregnancy after cancer treatments does not impair prognosis, even in hormone-dependent tumors such as breast cancer (Azim et al., 2013).

1.2. State of art

The most frequent gynecologic tumors (cervical, ovarian and endometrial cancer) represent 1,09 million new cancer cases worldwide, consisting of about 16% of tumors affecting women (Ferlay et al., 2015). Traditionally, gynecologic cancers are treated by radical surgery or with chemo and/or radiotherapy with definitive damage of reproductive capacity. For these patients, infertility is a dramatic and frequent side effect. Moreover, this severe and often underestimated complication heavily deteriorates the quality of life of patients and reduces treatment compliance (Partridge et al., 2014). Thus, fertility preservation plays a very important role that should be carefully evaluated in gynecologic cancer patients, integrating the best oncological treatment with discussion of the available strategies to avoid infertility. However, fertility-sparing strategies need a careful counseling (Borini et al., 2014). Benefits, risks and safety of fertility sparing procedures must be always balanced and discussed in referral centers.

1.3. Objective

In this review we highlighted the importance of oncofertility management for patients affected by gynecologic tumors, discussing some relevant issues, that have been largely debated in this field, posing particular attention to controversies and possible solutions. Thus, we focused the dissertation on uterine transplantation after cervical cancer, conservative surgery in early ovarian cancer, ovarian stimulation after serous borderline ovarian tumors, fertility preservation for patients with ovarian germ cell tumors, conservative management and progesterone treatment of early endometrial cancer. Table 1 illustrate and summarize key interventions to preserve fertility that we analyzed in the present review highlighting advantages and risks

2. Uterus transplantation after cervical cancer

Cervical cancer (CC) is the fourth most frequent tumor and the fourth cause of cancer deaths among women worldwide with a large majority of global burden occurring in the less developed regions, accounting for 12% of all female cancers (Ferlay et al., 2015). The discrepancy in terms of incidence and mortality between developed and developing countries is probably due to the different availability of screening programs. According to NCI guidelines, standard treatment consists of surgery in early tumors and of concomitant chemo–radiation in locally advanced disease. Being the uterus involved in all therapeutic procedures, the task of preserving fertility is in demand. In early stages, conservative strategies aimed to preserve fertility consist mainly of organ-sparing surgery, such as conization or radical vaginal/abdominal/mimimally invasive trachelectomy associated to laparoscopic pelvic lymphadenectomy (Fagotti et al., 2011; Pahisa et al., 2008; Pareja et al., 2013). Fertility-sparing surgery is usually indicated in patients with tumor diameter smaller than 2 cm. For patients with larger tumors who have a strong desire of preserving their fertility, some evidences have shown that neoadjuvant chemotherapy may allow tumor reduction and offer the chance of conservative surgery thereafter (Robova et al., 2014; Landoni et al., 2007). However, for more locally advanced stages the need of radical hysterectomy that may be followed by adjuvant chemo–radiation does not allow conservative management. When the uterus is removed, there is still the possibility of preserving the ovaries transposing them outside the radiation field, if this is indicated.

Oocytes might then be collected and, in case of the availability of a partner, allow embryo-transfer into a surrogate mother. The available motherhood options for women without uterus are adoption (to acquire legal motherhood), or pregnancy in a gestational surrogate carrier in order to acquire genetic motherhood, followed by adoption to acquire legal motherhood. Preclinical research of uterus transplantation was undertaken using several animal species, ranging from rodents to non-human primates (Brännström et al., 2012; Johannesson et al., 2013; Díaz-García et al., 2014). Fageeh W et al. and Ozkan O et al. carried out 2 cases of human uterus transplantation, one from cadaver and other from donor even if no clinical pregnancy has been reported (Fageeh et al., 2002; Ozkan et al., 2013). The first case resulted in an early uterine necrosis with the removal of this fully necrotic uterus 3 months after transplantation. The second case consisted of a uterus transplanted into a patient with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome who underwent embryo transfer 18 months after transplantation; unfortunately the patient had early miscarriage (Erman Akar et al., 2013). Recently, Brannstrom M et al. reported the results of the first clinical trial on uterine transplantation. Nine women were enrolled and all received the uterus from live donors. Eight patients had MRKH syndrome with congenital absence of uterus and vagina, the remaining 1 had previously undergone radical hysterectomy for CC of unspecified stage. All of them received immunosuppression to avoid rejection. Two of the nine women needed uterus removal after the first months, because of uterine artery thrombosis and severe intra uterine infection. The other seven women showed viable grafts and started to menstruate after 2–3 months post-transplantation, showing regular cycles during the first year. Occasional subclinical episodes of mild rejection were detected and confirmed by cervical biopsies, but were all effectively reversed by short courses of increased immunosuppression (Brännström et al., 2014a,b). Thus, the authors observed the outcomes among the 7 patients with viable uteri after uterus transplantation until a follow-up of 12 months. All of them showed regular menses and uterine artery blood flow unchanged. Four women showed mild inflammation highlighted through biopsies after mychophenolate mofetil withdrawal. All these women were treated with corticosteroids and azathioprine during the remainder of the 12 months. Subclinical rejections were founded on ectocervical biopsies in five recipients. However, all rejection episodes were successfully treated with corticosteroids or dose increments of tacrolimus (Johannesson et al., 2015). Recently, the same group reported the first live birth after uterus transplantation in a patient with Rokitansky syndrome (Brännström et al., 2014a,b). The uterus