

Fertility preservation in women with peritoneal surface malignancies: a case series

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ABSTRACT

The advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has improved survival in patients with peritoneal surface malignancies. Not surprisingly, there is now a growing interest on the possible means to preserve fertility to ensure future childbearing. In this study, we report on five women with peritoneal surface malignancies who performed ovarian hyper-stimulation and oocytes cryostorage prior to undergo CRS and HIPEC. The presence of the disease complicated follicular growth monitoring but the oocytes retrievals could be always performed and were uneventful. At last follow-up, all women were alive and disease-free. None has yet returned to thaw her oocytes. Overall, these cases suggest that oocytes cryopreservation before CRS and HIPEC should be considered.

Key words: Fertility preservation; oocyte; primary peritoneal disease; hyperthermic intraperitoneal chemotherapy; infertility; cytoreductive surgery

INTRODUCTION

Peritoneal surface malignancies are a rare group of pathologies which have been usually associated with a poor prognosis [1,2]. In female patients, since ovaries and uterus are often involved by the disease, a non conservative surgical approach is frequently necessary for complete cytoreduction, leading to menopause and permanent impossibility of childbearing [1,2]. However, innovative treatment approaches have recently allowed new hopes of cure, especially in younger women. Although evidence is still preliminary and no standard strategy can be advocated, an improved long-term overall survival has been reported in selected patient who underwent cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Aim of this approach is to obtain complete macroscopic cytoreduction with surgery and treat residual microscopic disease with intraoperative administration of HIPEC [1,2].

Not surprisingly, with a growing consent for this approach, there has been a wider interest on the potential impairment of the capacity of reproduction associated to CRS and HIPEC and the possible means to preserve fertility. In fact, natural conception can occur after this treatment provided that ovaries and uterus are spared, but this is rarely possible and the proportion of women achieving motherhood is inevitably very low [3].

On these bases, fertility preservation may deserve consideration in women with peritoneal surface malignancies prior to undergo CRS and HIPEC. However, available evidence is yet anecdotal [4-7] (Table 1). In this study, we report on five women with peritoneal surface malignancies who successfully underwent oocytes cryopreservation before surgery.

MATERIALS AND METHODS

All women attempting to perform oocytes cryopreservation at the Infertility Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy and who received oncological treatments at the Istituto Nazionale dei Tumori, Milan, Italy between 2013 and 2020 were retrospectively reviewed. Women could be included if they were diagnosed with peritoneal surface malignancies, including mesothelioma, pseudomyxoma peritonei and peritoneal carcinosis and if they were subsequently treated with CRS with HIPEC. Even if not strictly malignant, also benign mesotheliomas could be included because of their malignant behavior. Data were obtained from outpatients' charts. The study was approved by the Institutional Review Board. An informed consent to participate was not requested because of the retrospective design. However, all women in our units are routinely requested to sign an informed consent for their data to be used for research purposes and those denying this consent were excluded. The study is presented according to PROCESS guideline [8].

During the study period, young women (< 40 years) with cancers who required gonadotoxic treatments were routinely offered fertility counseling at the oncofertility service of the hospital. Women with peritoneal surface malignancies were included in this program regardless of the histology of the lesions. The service takes place once a week and is run by gynecologists who are expert in reproductive medicine. Women are counseled regarding the impact on future fertility of the planned treatments and the possible means to preserve fertility. The decision to perform oocytes cryopreservation is shared with the patient after taking into consideration also age, parity and results of the tests of ovarian reserve (Antimüllerian hormone – AMH and antral follicle count – AFC). This latter information is used to predict the chances to obtain a reasonable number of oocytes (at least 10 was considered a satisfactory target). Standardized random start protocols of ovarian hyperstimulation and oocytes cryopreservation were used, as described in details elsewhere [9,10]. Two weeks are generally necessary to complete a single cycle of oocytes retrieval. CRS and HIPEC

were performed as described in previous contributions [11]. Post-surgical follow-up consisted in physical examination and thoracic/abdominal CT-scan three-monthly during the first two years, and six-monthly afterward.

RESULTS

Five women were selected. Their main characteristics are illustrated in Table 1 [12]. Age varied between 22 and 30 years and all women were nulliparous. Diagnoses included mesothelioma in three cases (malignant in two of them), pseudomyxoma peritonei in one case and peritoneal carcinosis due to recurrent colon adenocarcinoma in one case. Only this latter case was a recurrent case, all the other were newly diagnoses. None had distant metastasis outside the abdominal cavity. In two women, more than one cycle of egg retrieval could be performed. Number of stored oocytes varied between 4 to 22. The retrievals were uneventful in all cases. Figure 1 illustrates one of these cases. After the retrievals, all included women underwent CRS with bilateral adnexectomy and HIPEC. The uterus was always spared. Surgery was as scheduled and histology confirmed in all women. Time between diagnosis and surgery varied between 9 and 30 weeks. At present all women are disease free but none has yet referred to thaw her oocytes.

DISCUSSION

CRS and HIPEC are extremely deleterious for subsequent fertility. In the vast majority of women, bilateral adenectomy is required (like in all our cases). Moreover, even when gonads are spared, intraperitoneal chemotherapy and the associated hyperthermia can both harm ovarian reserve (primordial follicles are typically located in the ovarian subcortical area, thus in close contact with the high temperature chemotherapeutic fluid). In addition, natural conception may be hampered by the severe adhesions that can develop after extensive surgery. Not surprisingly, pregnancies

following CRS and HIPEC are extremely rare. In a recent systematic review of the literature, Papageorgiou et al. identified only 14 cases [3]. None was obtained with the use of stored oocytes. These authors also failed to show an increased risk of obstetrical complications. To note, however, their sample size is insufficient for robust conclusions. It remains very important for those women to have a very careful pregnancy monitoring in order to achieve an uncomplicated obstetric result.

Overall, fertility preservation in women with peritoneal surface malignancies prior to CRS and HIPEC is reasonable. Oocytes can be obtained before the intervention and pregnancy course can be unremarkable. Women aged less than 40 with adequate ovarian reserve and who aim at future childbearing should be referred to oncofertility services to discuss fertility preservation prior to undergo surgery. Given the high chances of definitive and irreversible infertility after cancer treatment, we also advocate for more than one retrieval in order to maximize the potential chances of future pregnancies. The number of stored oocytes is directly related to the chances of pregnancy and to the number of children [13-15]. With the new modalities of ovarian hyperstimulation allowing to initiate treatment at any time of the menstrual cycle and combining cycles consecutively without pauses, two-three cycles can be performed without causing a significant delay to CRS and HIPEC [16,17]. In our experience, the number of stored oocytes varied between 4 and 22. Based on the model from Golman et al. [14], these numbers would correspond to chances of live birth varying between 37% and 90-95%. This data seems valuable even if it has to be underlined that the Golman's model is theoretical and has not been validated in the context of fertility preservation for oncologic reasons. Conversely, we deem unwise ovarian cortex freezing because of the risk of re-seeding the cancer at the time of re-implant.

This paucity of data on fertility preservation for peritoneal surface malignancies can be explained by the rarity of the condition and the poor prognosis, but, in our opinion, other factors may also contribute. We hypothesize that the enhanced difficulties of the oocytes retrieval may play a role. Ovaries can be displaced by the presence of the peritoneal disease and physicians may be concerned

by the need to transfix the peritoneal lesions during the retrieval. Moreover, ovaries could be difficult to be distinguished from the surrounding multicystic lesions, making the retrieval more demanding. Most peritoneal diseases are characterized by multiple or multilocular masses involving pelvic organs and peritoneum and ovaries can be difficult to identify. We were also initially concerned by these additional difficulties. However, after a multi-disciplinary discussion, we assumed that transfixion could not be expected to impact on the prognosis of the woman given that the disease is already diffuse on the whole peritoneal cavity. In addition, considering technical difficulties of discerning the dislocated ovary in the subverted pelvis, our experience showed that, in expert hands, this limitation is only theoretical. Ovaries could be identified in all cases and monitoring of follicular growth was not demanding. To note, identification of the ovary was progressively facilitated by follicular growth (Figure 1).

In conclusion, oocytes cryopreservation should be considered in young women with peritoneal surface malignancies scheduled for CRS and HIPEC. International oncological guidelines recommend that all patients diagnosed with cancer in reproductive years should discuss with a specialist the possible consequences of the disease and its treatment on their future fertility and the possible options to counteract these effects [18]. Peritoneal surface malignancies should not be an exception.

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Figure legend

Figure 1: Case 3. The woman was diagnosed with multicystic benign mesothelioma. Distinguishing the ovary from the surrounding multicystic lesion that occupied the pelvis may be initially challenging. This task becomes easier with the follicular growth. This US image was taken on day 6 of stimulation and the increased diameter of the growing follicles (highlighted with the small white asterisks) facilitated the identification of the ovary. To improve the reliability of the scans and the safety of the whole procedure, we recommend that all ultrasounds are performed by the same expert physicians who will also perform the oocytes retrieval.