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FERTILITY PRESERVATION

Ovarian stimulation during the luteal phase for fertility preservation of cancer patients: case reports and review of the literature

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Abstract
Purpose To report the case of a patient with a diagnosis of infiltrative ductal carcinoma of the breast (case 1) and of a patient with Hodgkin's lymphoma (case 2), both submitted to ovarian stimulation during the luteal phase of the menstrual cycle in order to cryopreserve embryos and oocytes, respectively, in view of the need to start chemotherapy within a maximum of three weeks.
Methods Case reports
Results Both patients were submitted to ovarian stimulation with recombinant follicle stimulating hormone together with pituitary blockade with a GnRH antagonist during the luteal phase of the cycle. Oocyte retrieval was performed nine days after the beginning of ovarian stimulation, with 12 mature oocytes being obtained in both cases. In case 1, all mature oocytes were submitted to ICSI, with fertilization and cleavage rates of 83.3% and 70%, respectively, and with the formation of seven good quality embryos. In case 2, all of mature oocytes were cryopreserved.
Conclusions These cases demonstrate that it is possible to obtain mature oocytes when ovarian stimulation is started in the luteal phase in situations in which there is not sufficient time for conventional stimulation.

Capsule We report two cases of successful oocyte retrieval in cancer patients whose stimulation was started in the luteal phase.

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Introduction

In the U.S., the estimate of new cases of breast cancer affecting the female population younger than 45 years was 78,580 in 2009 [1], reflecting an important incidence of the disease during the reproductive phase.

The increased survival afforded by the development of oncologic therapy elicits growing interest on the part of the patients in the preservation of quality of life and of their reproductive potential after the end of treatment. However, these patients frequently face the consequences of chemotherapy and/or pelvic radiotherapy such as premature ovarian failure and infertility [2]. This has led oncologists and specialists in human reproduction to consider offering as early as possible techniques aiming at attempted preservation of fertility. Assisted reproduction techniques can also be used in patients at risk for impaired ovarian reserve due to ovarian surgery or treatment of benign diseases such as systemic lupus erythematosus and other autoimmune diseases such as immune thrombocytopenic purpura and microscopic polyangiitis [3].

Among the strategies for the preservation of fertility, embryo cryopreservation appears to be the most effective approach. If various embryos are frozen, the cumulative pregnancy rates can reach 60% [4]. However, standard regimens of ovarian stimulation are started during the early follicular phase of the menstrual cycle or after pituitary blockade with gonadotropin releasing hormone (GnRH) for 10 days or more. Thus, if the patient is in the luteal phase of the menstrual cycle at the time when the option for ovarian stimulation is made for subsequent oocyte or embryo

cryopreservation, the treatment may extend over a total of up to six weeks which, in some cases, is unacceptable due to the need for early chemotherapy and/or radiotherapy.

For patients without a partner, oocyte cryopreservation before chemotherapy and/or radiotherapy should be considered in an attempt to preserve future fertility. However, the success rate can be four times lower than that observed with embryo cryopreservation [5]. This approach also requires a certain period of time for ovarian stimulation when the standard protocols of stimulation mentioned above are followed.

Some studies on small patient series have used treatment with a GnRH analogue during cytotoxic therapy for preservation of ovarian function. The American Society of Clinical Oncology has stated that current evidence is insufficient regarding the safety and efficacy of GnRH analogues and of other methods of ovarian suppression for the preservation of fertility. The Society recommends that women interested in ovarian suppression treatment be encouraged to participate in clinical studies [6].

There are situations in which, due to the imminent necessity of starting a cytotoxic treatment, it is not possible to schedule the beginning of ovarian stimulation during the early follicular phase of the menstrual cycle or after pituitary blockade with GnRH agonists. In these cases, some investigators have raised the possibility of cryopreservation of ovarian tissue for future orthotopic or heterotopic reimplantation, although the international experience is limited and unsatisfactory results have been reported regarding the occurrence of pregnancy [7]. An alternative, also of an experimental nature, is the cryopreservation of immature oocytes, a technique associated with a low pregnancy rate and with high abortion rates [8].

In view of these considerations, a possible perspective is to consider the possibility of performing ovarian stimulation even in the luteal phase of the menstrual cycle, as long as the pituitary is blocked with a GnRH antagonist 3 to 4 days before the procedure [9] or concomitantly with the beginning of ovarian stimulation with gonadotropins. The data reported in the present pilot study suggest that oocytes may be obtained before the beginning of cancer treatment regardless of the phase of the menstrual cycle during which ovarian stimulation is started [9].

We report here two cases of patients in menacme seen at the Assisted Reproduction service of the University Hospital of Ribeirão Preto. The patients had a diagnosis of malignant neoplasias requiring the initiation of chemotherapy within a maximum of three weeks and were in the luteal phase of the menstrual cycle at the time when the possibility of attempted preservation of fertility was presented to them. Both patients opted to start ovarian stimulation with gonadotropins during the luteal phase of the cycle concomitantly with the use of a GnRH antagonist, with a satisfactory response in terms of follicle growth, number of mature oocytes obtained and of embryos formed, as described in the reports below.

Case report

Case 1

A 31-year-old married patient, G2P1A0 (cesarean delivery 11 months ago), with invasive ductal carcinoma of the left breast (with positive estrogen receptors in less than 10% of the cells) manifested her wish to cryopreserve embryos before starting chemotherapy, scheduled to begin after three weeks. Cetrorelix (Serono, 0.25 mg/day), recombinant follicle stimulating hormone (FSHr, Puregon, Shering-Plough, 300 IU/day) and recombinant luteinizing hormone (LH, Luveris, Serono, 75 IU/day) were started concomitantly on the 17th day of the menstrual cycle. After seven days of daily use of the medications, ultrasound monitoring revealed 11 follicles with a mean diameter ≥17 mm. On the 7th day, human recombinant chorionic gonadotropin (hCG) (Ovidrel, Serono, 250 μg) was administered at 10:00 pm. Thirty-five hours after hCG administration, ultrasound-guided oocyte retrieval was performed by the transvaginal route under general anesthesia. Thirteen cumulus oophorus complexes were obtained. Oocyte denudation was performed about three hours after oocyte retrieval, revealing 12 mature oocytes that were submitted to intracytoplasmic sperm injection (ICSI). Fertilization was analyzed approximately 19 h after ICSI, with 10 normally fertilized oocytes being detected (an 83.3% fertilization rate). Seven of the 10 oocytes fertilized cleaved (a 70% cleavage rate), progressing to the formation of seven embryos of good quality (six cells or more and less than 20% fragmentation). The embryos were cryopreserved on the third day of development (five of them with eight cells, three of which with absence of fragmentation and two with less than 20% fragmentation). The patient started chemotherapy 18 days after her first visit to the Assisted Reproduction service, 14 days after the beginning of the cycle of ovarian stimulation for ICSI.

Case 2

A 24-year-old single patient with no sex partner, nulligravida, with Hodgkin's lymphoma of the nodular sclerosis type manifested the wish to cryopreserve oocytes before starting chemotherapy scheduled to begin within a maximum of three weeks. She had regular menstrual cycles without the use of hormonal contraceptives and was in the 22nd day of the menstrual cycle when she started controlled ovarian stimulation for oocyte cryopreservation. Orgalutran

(Shering Plough; 0.25 mg/day) and FSHr (Gonal®, Merck Serono, 225 IU/day) were started simultaneously on the 24th day of the menstrual cycle. After seven days of daily use of the medications, ultrasound monitoring revealed 8 follicles with a mean diameter ≥14 mm, 4 of which had a mean diameter ≥17 mm. hCG (Ovidrel, Serono, 250 μg) was administered on the 7th day at 10:00 pm. Thirty-five hours after hCG administration, ultrasound-guided oocyte retrieval was performed by the transvaginal route under general anesthesia. Thirteen cumulus oophorus complexes were obtained, containing 12 mature oocytes of good quality as determined by morphological criteria, and cryopreserved. She started chemotherapy 22 days after her first visit to the Assisted Reproduction service.

Discussion

Ovarian follicular development resulting in the ovulation of a single mature oocyte is a complex process coordinated by stimulating and inhibitory autocrine, paracrine and humoral factors [10], still incompletely understood today.

The traditional concept of folliculogenesis supports the recruitment of various antral follicles in each ovary during the late luteal phase of the preceding menstrual cycle [11]. A single follicle is selected during the beginning or the middle stage of the follicular phase, while the others undergo atresia [12]. However, some studies have demonstrated that the small antral follicles observed in the luteal phase may not necessarily be in atresia, but may rather be in the early stages of follicular development. This indicates waves of follicular development within a single interovulatory period [13], with the presence of healthy follicles in the luteal phase of the menstrual cycle as determined by oocyte and granulosa cell viability [14].

Patients in menacme who wish to preserve fertility and who must start cytotoxic treatment soon after adiagnosis of cancer may not have sufficient time to be submitted to standard controlled ovarian stimulation starting in the early follicular phase or after pituitary blockade with GnRH agonists (a procedure that usually lasts 10 or more days). In addition, the possible reduction of effectiveness of in vitro fertilization after each chemotherapy cycle is recognized, reinforcing the importance of discussing early with the patients the strategies available for attempted preservation of fertility, to be preferentially initiated before the beginning of cytotoxic treatment [15].

The data presented here for the two patients reported demonstrated that ovarian stimulation starting in the luteal phase of the menstrual cycle concomitantly with pituitary blockade with a GnRH antagonist lasted on average seven days, a fact that did not cause postponement of the beginning of the recommended chemotherapy. Both patients presented a satisfactory response to ovarian stimulation, with 12 mature oocytes being retrieved. The married patient opted for the cryopreservation of embryos, a technique available at many assisted reproduction services in Brazil, with seven embryos of good quality being produced and cryopreserved on the third day of development. The patient with no sex partner opted for oocyte cryopreservation, a technique still considered to be experimental but whose diffusion has substantially increased over the last few years in parallel to the improved results of assisted reproduction associated with the use of cryopreserved oocytes [16, 17]. The data presented here agree with those of a recently published study [18] which demonstrated the possibility of obtaining oocytes from 12 cancer patients submitted to ovarian stimulation starting in the luteal phase of the menstrual cycle. In that study, pituitary blockade with a GnRH antagonist was started concomitantlty with FSHr administration. Ovarian stimulation with gonadotropins lasted on average 11.4 days, without compromising the proposed beginning of chemotherapy for the patients studied. A mean number of 10 oocytes were obtained, 80.4% of them being mature (approximately 8 mature oocytes). Fifty-one oocytes obtained from patients stimulated during the luteal phase were submitted to ICSI, with a 75.6% rate of fertilization. When these data were compared to those of cancer patients submitted to standard protocols of ovarian stimulation starting during the follicular phase of the cycle, no significant differences were observed regarding the total gonadotropin dose used, the duration of ovarian stimulation, the mean number of oocytes retrieved, or the rates of oocyte maturation and fertilization.

The cases reported here suggest that ovarian stimulation during the luteal phase of the menstrual cycle can be successfully performed and should be considered for patients who are in the luteal phase of the cycle at the time when they opt for the use of strategies aiming at the preservation of fertility and who do not have sufficient time to start standard ovarian stimulation in the follicular phase of the cycle or after pituitary blockade with GnRH antagonists. Additional clinical studies are needed to assess the efficacy of this strategy, especially regarding the rates of clinical pregnancy and of liveborn infants originating from the use of cryopreserved embryos and of oocytes obtained by ovarian stimulation during the luteal phase of the cycle.

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