Successful transfer of frozen-thawed embryos obtained after subtotal colectomy for colorectal cancer and before fluorouracil-based chemotherapy

Foad Azem, a,* Ami Amit, a Ofer Merimsky, b and Joseph B. Lessing a

a The Sara Racine IVF Unit, Tel Aviv Sourasky Medical Center, Lis Maternity Hospital, Tel Aviv, Israel

b The Soft Tissue and Sarcoma Oncology Unit, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Abstract

Background. Fertility preservation is applied to patients with cancer who may be rendered sterile from chemotherapy or radiotherapy. Fluorouracil is considered as having almost no effect on human reproductive function, although clinical data defining infertility risk is negligible.

Case. Controlled ovarian stimulation, in vitro fertilization (IVF), and embryo freezing were performed before fluorouracil-based chemotherapy in a 28-year-old woman who underwent subtotal colectomy for colorectal cancer (CRC). Three years later, when the clinical and hormonal analysis confirmed ovarian failure, two thawed embryos were transferred to the uterus. She gave birth at term to a 3200g infant.

Discussion. Women with good prognosis who wish to bear children in the future should be offered fertility preservation options before chemotherapy, even if the likelihood of permanent ovarian failure appears to be negligible.

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Introduction

Because of advancements in fertility sparing technologies and improved oncology outcomes, fertility preservation for young patients scheduled to undergo chemotherapy or radiotherapy has increased importance. In post-pubertal males, preservation of fertility is achieved simply by freezing sperm samples before treatment. In women, fertility preservation options include oocyte or embryo cryopreservation and, recently, ovarian tissue cryopreservation (OTCP) [1,2]. The decision as to which procedure to recommend depends upon the primary malignancy, protocol of chemotherapy, age, and marital status of the patient.

Alkylating agents, especially cyclophosphamides, are well known for their destructive potential for ovarian failure [3]. Fluorouracil is considered as having almost no effect on human reproductive function, although clinical data defining infertility risk is negligible [4].

The present early report suggests that 5-Fluorouracil (5-FU) can be a castrating drug even when administered as a single regimen. We contend that fertility preservation should be offered to all women with good prognosis who are interested in bearing children in the future and in whom the therapeutic regimen upon which they are about to embark may render them sterile. Our report highlights the importance of providing suitable patients with sufficient information on the risks and benefits of the available treatment options to involve them in decisions on fertility preservation before chemotherapy.

Case report

Patient

A 28-year-old married nullipara woman was referred for consultation to the Fertility Preservation Clinic before...
starting chemotherapy. She had just undergone a subtotal colectomy because of high-grade colon cancer (stage B2 according to modified Asler Coller scale [MAC]). Family history revealed that her father had been diagnosed at 40 years of age as suffering from CRC. Her sister underwent total colectomy because of CRC 1 year later. The patient and her sister were diagnosed as being carriers of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome mutation.

Methods

The patient’s planned chemotherapeutic regimen included 5-FU/leucovorin. The various cryopreservation options were explained to her and her husband. Because she fortuitously presented on the third day of her menstrual cycle, we could advise the couple to undergo in vitro fertilization (IVF) and embryo cryopreservation for the preservation of fertility without putting her at risk by delaying chemotherapy for only 2 weeks. Four oocytes were retrieved, and three embryos were fertilized and cryopreserved at the 2 PN stage. The Institutional Ethical Committee approved the embryo cryopreservation procedure as well as the freezing protocol. The patient was started on 5-FU 425 mg/m²/day and leucovorin 20 mg/m²/day on days 1–5 every 28 days. The treatment was changed to once weekly due to severe gastrointestinal toxicity and oral mucositis. The severe gastrointestinal toxicity resolved but reappeared 5 weeks later, and the protocol was changed to fltorafur 200 mg/day for 4 months. This treatment continued uneventfully and was terminated on January 2001. Monthly intramuscular injections of triptorelin embonate 3.75 mg (Decapeptyl Depot; Ferring GmbH, Kiel, Germany) were administered in conjunction with the chemotherapy. The patient was disease-free for more than 3 years thereafter.

Upon termination of chemotherapy, the patient started to experience hot flashes and her gonadotropin levels were consistent with premature ovarian failure 4 months later. Hormone replacement therapy (HRT) was initiated, but she was still in a menopausal state after 2 years of treatment. Three years after surgery, positron emission computed tomography (PET-CTS) disclosed no evidence of disease, and the blood carcinoembryonic antigen (CEA) levels, liver enzymes, and blood chemistry were within normal limits. She now expressed a desire to become pregnant. After consultation with the institutional oncologists, preparation of the endometrium was based on administration of 2 mg (tid) of E2 valerate (Progynova; Schering Health Care Ltd., West Sussex, UK). Vaginal administration of micronized progesterone (200 mg tid, Utrogestan; Besins International Laboratories, Paris, France) was added to the drug regimen when endometrial thickness reached 8 mm. Seventy-two hours later, the two surviving thawed embryos were transferred, and 12 days later, her hCG was 112 IU and doubled within 48 h. She experienced vaginal bleeding during the first 6–7 weeks of gestation, and on the ninth gestational week, she underwent laparotomy after diagnosed as carrying heterotopic pregnancy. She underwent right salpingectomy and the post-operative course was uneventful. Upon surgery, pelvic adhesions were documented involving two small ovaries. Ultrasonographic survey disclosed a healthy fetus, and she gave birth at term to a healthy 3200g infant.

Discussion

Most clinical reports on cytotoxic drug-induced sterility are based on retrospective reports of women who were mainly treated with alkylating agents. One of them, cyclophosphamide, is the cause of most severe germ cell dysplasia in both male and female humans [3].

Currently, embryo cryopreservation offers the most promising option for fertility preservation [1]. This option, however, requires controlled ovarian stimulation and synchronization with the onset of the menstrual cycle. Oocyte cryopreservation shares similar drawbacks and carries the further risk of significantly lower fertilization and pregnancy rates [1]. Transposition of ovaries is another fertility-preserving procedure that should be considered in women before scheduled pelvic radiotherapy without chemotherapy, that is, for early-stage cervical cancer [5]. OTCP has been suggested mainly in young women whose ovaries would most probably be destroyed by chemotherapy. It can be performed immediately because it is unrelated to the menstrual cycle and is suitable for young children, girls, and unmarried women [2]. 5-Fluorouracil (5-FU), belongs to the antimetabolite class of chemotherapy and inhibits the cellular metabolites by acting as a false substrate for reactions required in DNA or RNA synthesis (the S-phase of the cell cycle) [6]. 5-FU acts against epithelial malignancies arising in the gastrointestinal tract, breasts, as well as the head and neck. 5-FU/leucovorin chemotherapy is the standard protocol for colorectal cancer (CRC). The benefits of adjuvant chemotherapy after curative resection of Stage III CRC have been clearly demonstrated [7]. Many of the side effects of 5-FU affect rapidly dividing cells, such as bone marrow, intestinal mucosa, embryo and germ cells. The side effects are dose-dependent, and myelotoxicity is the major toxic effect in patients receiving bolus doses. Hand–foot syndrome (palmar–plantar erythrodysesthesia), stomatitis, neuro- and cardiotoxicity are associated with continuous infusions and oral pyrimidines. Other adverse effects associated with both bolus dose and continuous infusion regimens include nausea and vomiting, diarrhea, alopecia, and dermatitis [7]. It was shown that 5-FU is teratogenic to the rapidly dividing rodent embryo, and toxic to differentiated and
stem spermatogonia [8]. Recently, fertility toxicity in mice was reported to be cycle-dependent, but 5-FU has been regarded as having almost no effect on human reproductive function [4].

5-FU as a single agent caused necrosis and spread damage to treated gonads of Locusta migratoria [9]. Data are lacking on the incidence of amenorrhea in humans associated with the single 5-FU regimen, and an increased risk of germ cell damage caused by a single-dose regimen of 5-FU is not well defined [4]. In the adjuvant setting, 5-FU and methotrexate are associated with a 9% incidence rate of amenorrhea, compared to 69% in the combined regimens, such as cyclophosphamide, methotrexate, and 5-FU (CMF) [10].

In this reported case, the patient and her sister were carriers of HNPCC; to the best of our knowledge, there is no reported association between HNPCC and premature ovarian failure. Furthermore, they had no family history of premature ovarian failure. Her sister had completed chemotherapy but now has irregular menstrual cycles. Information on her hormonal status, however, is lacking.

The present early report demonstrates that 5-FU and leucovorin followed by fluorafur (as a single agent) can cause premature ovarian failure in humans. To the best of our knowledge, this is the first reported case of ovarian failure in a human as a result of 5-FU-based treatment. Undergoing an immediate IVF and embryo-freezing procedure successfully preserved the fertility in our patient, even though she was at low risk of ovarian failure and sterility due to the proposed chemotherapeutic protocol. Our experience emphasizes the importance of notifying patients of the potential risk of iatrogenic sterility as early as possible. Once the diagnostic process and clinical stage have begun, if there is a “window of opportunity” in terms of the woman’s menstrual cycle, it should be used to initiate and complete the appropriate fertility preservation option since oocyte and embryo cryopreservation are synchronized with the onset of the menstrual cycle. Timing is key to the feasibility of affording the option of fertility preservation before the initiation of radiotherapy or chemotherapy and so we urge physicians to bear in mind that:

- Chemotherapy, even 5-FU-based, may lead to ovarian failure.
- There are now several methodological options for preserving fertility.
- For a woman with good prognosis and interested in bearing children in the future, timing is of the essence for carrying out the procedure and doing so without putting her at risk by delaying essential radiotherapy or chemotherapy.

References