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Case Series

Pregnancy Outcome from an Oocyte Retrieval Following Chemotherapy for Breast Cancer

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Abstract

As mortality rates for reproductive age cancer patients improve, it is vital to understand how treatments such as chemotherapy reduce reproductive potential. Fertility preservation before gonadotoxic chemotherapy initiation is not always possible when treatment must start as soon as possible. There are minimal data regarding pregnancy in patients who have undergone fertility preservation after chemotherapy and subsequently delivered from cryopreserved embryos. Here we report two cases of patients with breast cancer who underwent ovarian hyperstimulation and embryo cryopreservation within 12 months of chemotherapy. The first patient was diagnosed with triple negative invasive ductal carcinoma and underwent oocyte retrieval 6 months after her last dose of chemotherapy. Via gestational carrier, a term healthy infant was born. The second patient was diagnosed with hormone receptor negative, HER-2 positive invasive ductal carcinoma and underwent oocyte retrieval 2 months after her last dose of chemotherapy. Her frozen embryo transfer did not result in pregnancy. To our knowledge, this is the first report on embryo transfer outcomes in women with breast cancer using embryos cryopreserved within a year of chemotherapy exposure.

Keywords: Oncofertility, Fertility preservation; Chemotherapy; Breast cancer; Oocyte retrieval; Embryo transfer

Abbreviations: IVF: *In vitro* Fertilization; AMH: Antimullerian Hormone; AFC: Antral Follicle Count; BMI: Body Mass Index; FET: Frozen Embryo Transfer Cycles; hCG: Human Chorionic Gonadotropin; E2: Estradiol; PGT-A: Preimplantation Genetic Testing for Aneuploidy

Introduction

The probability of being diagnosed with invasive cancer during a woman's reproductive years is 5.8% [1]; for breast cancer the probability is 2.1% [1]. The overall incidence of breast cancer has increased by 0.5% annually from 2014 to 2018, but mortality rates have continued to decline, with the 5-year relative survival rate now at 90% [1]. This reduction in mortality rates is likely due to earlier detection and continued improvements in treatment. However, the same treatments that are improving overall survival, such as chemotherapy, are known to be gonadotoxic and can reduce reproductive potential [2,3]. The Practice Committee of the American Society for Reproductive Medicine recommends that care teams provide prompt counseling regarding options for fertility preservation such as ovarian hyperstimulation and cryopreservation of oocytes or embryos before undergoing fertility-threatening cancer treatment [4]. However, fertility preservation before treatment initiation is not always possible when chemotherapy must be started immediately, such as in aggressive or high stage malignancies. In these cases, patients have the option of ovarian tissue cryopreservation before chemotherapy or oocyte and/or embryo cryopreservation after chemotherapy.

Chemotherapy regimens damage oocytes by directly affecting the follicles and damaging surrounding somatic cells [5]. Anti-metabolite chemotherapeutics primarily affect developing follicles while cell cycle-independent agents, such as alkylating agents and topoisomerase inhibitors, primarily affect the primordial follicles which comprise the dormant follicular pool [6]. Chemotherapeutic agents reduce ovarian reserve by inducing DNA damage in the oocyte, which can result in cellular apoptosis, and by increasing follicular recruitment and depletion [7,8].

In humans, progression from a primary follicle to ovulation takes approximately 85 days [9]. Therefore, some recommend that patients delay fertility preservation procedures until 6-12 months after the conclusion of chemotherapy [10]. Studies investigating outcomes of children born to childhood cancer survivors are reassuring with no evidence of increased risk of chromosomal abnormalities or birth defects compared to controls [11-13]. However, the exposure to chemotherapy and subsequent reproduction in these cases is often many years or decades. In one large registry study of patients receiving chemotherapy as adults, the authors found a 2-fold increased risk of preterm birth and low birth weight for women who conceived within one year of chemotherapy treatment compared to those who waited at least one year to conceive [10]. However, the rate of birth defects was not reported and as the study linked live birth data to a cancer registry, there are no data on miscarriage rates. Animal studies have shown increased rates of malformation and chromosomal abnormalities in the offspring of mice that have received chemotherapy compared to controls, with a return to normal rates after 12 weeks; in this species follicular maturation takes 3 weeks [14,15].

When chemotherapy cannot be postponed, we believe that patients should be offered oocyte or embryo cryopreservation during a break in treatment or during a remission phase. There are limited data regarding miscarriage and malformation rates in patients who have undergone fertility preservation after chemotherapy [16]. Here we report two cases of patients with breast cancer who underwent ovarian hyperstimulation and embryo cryopreservation within 12 months of chemotherapy.

Case Presentation

Patients included in this case report were identified by searching the electronic medical record at Brigham and Women's Hospital Center for Infertility and Reproductive Surgery from January 2012 through January 2020. All patients who underwent ovarian hyperstimulation and oocyte retrieval for a new cancer diagnosis and subsequently returned for embryo transfer (autologous or using a gestational carrier) were included. A total of 48 patients with 71 individual frozen embryo transfer (FET) cycles were identified. Two patients underwent ovarian hyperstimulation and oocyte retrieval less than one year following chemotherapy treatment and are presented here.

The clinical protocol for ovarian hyperstimulation, oocyte retrieval and embryo transfer for both patients was as follows. Standard controlled ovarian hyperstimulation and monitoring protocols were used. Gonadotropin doses were determined based on age, serum antimullerian hormone (AMH) levels, antral follicle count (AFC), and body mass index (BMI. Ovarian stimulation was performed with the use of exogenous gonadotropins (Gonal-F, EMD-Serono; Menopur, Ferring Pharmaceuticals). Pituitary suppression was attained with the use of GnRH antagonist (Ganirelix, Organon USA). Gonadotropin dosage was adjusted according to each patient's response to stimulation, which was monitored with the use of transvaginal ultrasounds and serial estradiol levels. When at least two follicles reached a mean diameter of 18mm, final oocyte maturation was triggered with the use of human chorionic gonadotropin (hCG) (10,000 units intramuscular (Pregnyl, Merck) or 250 mcg subcutaneous (Ovidrel, EMD-Serono). Ultrasound-guided transvaginal oocyte retrieval was performed 36 hours after trigger under anesthesia.

All gametes and embryos were cultured at 37°C in a dry incubator under an atmosphere of CO_2 (5-6%), O_2 (5%), and N_2 (89-90%). Conventional insemination was performed 4-6 hours after oocyte retrieval, followed by a fertilization check 16-18 hours after fertilization. Two pronuclear (2pn) zygotes were cryopreserved using standard vitrification protocols. Patients underwent a freeze-all cycle and had subsequent frozen embryo transfer (FET) cycles. At the time of FET cycle, 2pn zygotes were thawed using standard protocols and cultured until day 3 (cleavage stage). Embryos were graded on day 3 based on the number of cells present, degree of fragmentation (0 – none, 1 – slight (<10%), 2 – moderate (10-25%), 3 – severe (25-49%), 4 (>50%)) and symmetry (1 – symmetric, 2 – slightly asymmetric, 3 – severely asymmetric). Grades reported as #.## (cells.fragmentation/symmetry). Both patients underwent medicated FET cycles. Estradiol (E2) was supplemented with tablets (Estrace, TEVA Pharmaceuticals) given orally or vaginally, and/or using estradiol patches (Climera, Bayer Pharmaceuticals). Following at least 14 days of E2 administration, and once adequate endometrial thickness was achieved (7mm), daily intramuscular progesterone (25 mg on the first day then increased to 50 mg daily, AuroMedics Pharma LLC) was initiated. The serum progesterone level was checked on the day of transfer, and if < 20 ng/mL, dosing was increased to reach a level of ≥ 20 ng/mL.

Case 1

Case 1 was a 32-year-old G0 woman who presented for fertility preservation in the context of Stage II metastatic triple negative invasive ductal carcinoma and BRCA1 mutation. She received neo-adjuvant chemotherapy with 4 cycles every two weeks of Adriamycin (60 mg/m^2) and Cytoxan (600 mg/m^2) followed by Taxol (175 mg/m^2) every two weeks. She had a severe hypersensitivity reaction with her third Taxol treatment and was switched to Abraxane (260 mg/m^2) for her last cycle (cycle 4). She then underwent bilateral mastectomy followed by adjuvant radiation therapy which was completed three months following her surgery.

The patient was first seen for fertility preservation consultation at the time of her breast cancer diagnosis. She was treated with a GnRH-agonist (Lupron) during chemotherapy for ovarian protection. Her periods returned promptly and were regular following the end of chemotherapy. She was then seen 6 months

following her last chemotherapy dose to proceed with an embryo banking IVF cycle with the goal of using a gestational carrier in the future. Her AMH was 0.5 ng/mL and antral follicle count was 5 before oocyte retrieval. Her partner's sperm parameters on semen analysis were normal. Ovarian hyperstimulation was accomplished using 300 IU Gonal-F daily starting on cycle day 2. On cycle day 6, she was started on 250mg Ganirelix for prevention of ovulation. She was triggered with 10,000 IU of human chorionic gonadotropin when 12 follicles were measurable (3 in the right ovary and 9 in the left ovary) on cycle day 12. Fifteen oocytes were retrieved, 10 metaphase-II (MII) mature oocytes were inseminated, 5 fertilized normally and were vitrified at the 2pn stage on day 1.

Fifteen months after oocyte retrieval and embryo banking, the patient requested FET using a gestational carrier. At this time, her disease progressed and she had limited life expectancy. A multidisciplinary team including Reproductive Endocrinology, oncology and social work counseled her extensively and the team agreed to allow her to proceed with a gestational carrier FET cycle. Uterine preparation was accomplished using 3 mg of oral estrace twice a day. On day 14 of her cycle, endometrial thickness was noted to be 9.3mm and progesterone level was 0.39 ng/mL after 14 days of estradiol. She was started on IM progesterone in oil and the next day three 2pn zygotes were thawed and cultured to day 3. Two cleavage-stage embryos were transferred per clinic protocol (grades: 4.13 and 9.12) and the third embryo (grade 2.32) was cultured out to days 5-6, but it failed to blastulate and was discarded. Thirteen days following embryo transfer, serum hCG level was 161 IU/L. Repeat hCG levels rose normally and a single intrauterine pregnancy was diagnosed. She delivered a healthy male infant at term weighing 7 pounds and 1 ounce.

Case 2

Case 2 was a 38-year old G5P1041 woman with a history of a full term delivery following IVF, who presented for fertility preservation in the context of Stage II hormone receptor negative, HER-2 positive invasive ductal carcinoma. She was pregnant at the time of diagnosis after conceiving in her second cycle of IVF. She underwent pregnancy termination at 7.3 weeks in the context of the concern of risks involved with her cancer treatment. She began Trastuzumab (8 mg/kg), Pertuzumab (840 mg), and paclitaxel (80 mg/m^2) daily for 12 weeks. She then underwent left total mastectomy with level 1 and 2 axillary lymph node dissection and immediate reconstruction. Postoperative chemotherapy was begun 4 weeks after surgery as is standard, allowing time for an IVF cycle for fertility preservation prior to starting chemotherapy.

Her AMH 2 months prior to starting neo-adjuvant chemotherapy was 0.78 ng/mL and a repeat level one month prior to completing neo-adjuvant chemotherapy (two months prior to her IVF cycle), was undetectable. Her partner's sperm parameters were normal. She underwent IVF cycle one month following her last neo-adjuvant chemotherapy dose and two weeks following her surgery. Ultrasound demonstrated two antral follicles. Ovarian hyperstimulation was accomplished with 450 IU Gonal-F and 2 ampules of Menopur daily. She was started on 250 mg Ganirelix on cycle day 8 and was triggered with 250 mcg of hCG (Ovidrel) on cycle day 18 when 3 follicles were measurable (1 in right ovary, 2 in left ovary). Four oocytes were retrieved, three were mature and were inseminated. One MII oocyte fertilized and was vitrified at the 2pn stage. Following her IVF cycle, she received 4 cycles of adjuvant chemotherapy with dose dense cyclophosphamide (600 mg/m^2) and doxorubicin (60 mg/m^2). She then underwent radiation treatment and began trastuzumab (6 mg/kg) every 3 weeks for nine months.

The patient returned for frozen embryo transfer 14 months after chemotherapy was completed. Baseline estradiol and progesterone were "Less than assay" and 0.06 ng/mL, respectively. Uterine preparation was begun using 2 mg of oral estrace twice daily and 0.1 mg estradiol patch every three days based on a previous prep cycle. Ultrasound on cycle day 15 demonstrated an endometrial thickness of 12.9 mm and her progesterone was 0.13 ng/mL and IM progesterone in oil was begun. On cycle day 18, one day 3 cleavage-stage embryo (grade 4.12) was transferred. The cycle did not result in pregnancy.

Discussion and Conclusions

Most providers recommend delaying conception for 6-12 months after receiving chemotherapy due to the concern that chemotherapy may damage oocytes, which could lead to an increased risk of miscarriage and birth defects [10]. It is not always possible to delay chemotherapy prior to fertility preservation. Little data exists in the literature examining fertility preservation outcomes in patients who undergo fertility preservation procedures shortly after chemotherapy. As such, the concerns of increased risks of miscarriage and birth defects are theoretical. We found only one other case report on embryo transfer outcome for a patient who underwent in oocyte retrieval after induction chemotherapy with daunorubicin and cytarabine for AML treated. She underwent embryo transfer 2 years and 2 months later and delivered a term infant [17].

The effects of specific chemotherapeutic agents on oocytes in vivo have mostly been studied in non-human models [5]. Cyclophosphamide and doxorubicin (both received by the patient in case 1) are known to cause double stranded breaks in DNA of primordial follicle oocytes which can lead to cell death [5]. In mice, cyclophosphamide treatment led to higher rates of pregnancy failure and malformation compared to controls [15]. With an increased interval between chemotherapy exposure and conception (3 months), the malformation rate returned towards baseline values [15]. However, given species specific factors in folliculogenesis and oocyte development, it is not possible to make

a linear correlation in timescale of follicular maturation between mice and humans [18]. While in vitro studies have shown depletion of primordial follicles with the use of doxorubicin and taxanes (both received by the patient in case 1), there are no data on rates of miscarriage or birth defects following their use [5,19,20]. Little is known about newer monoclonal antibody agents that the patient in case 2 received regarding their effects on the ovary and fertility. Most of the data on these agents comes from limited case reports of women who incidentally became pregnant while on adjuvant treatment with these agents and outcomes report healthy term infants as well as some cases of oligohydramnios [21].

Given the gonadotoxic effects of many chemotherapeutics, genetic alterations could occur in oocytes that have been exposed to these agents, which could in turn theoretically lead to miscarriage or congenital malformations. Most in vitro studies describe apoptotic cell death and follicular activation/depletion as the methods of chemotherapy-induced ovarian damage, as opposed to genetic damage of the oocyte, but in vivo studies are limited [22]. Pre-implantation genetic testing for aneuploidy (PGT-A) could be undertaken to evaluate for chromosome abnormalities, but this technology has not been proven to reduce miscarriage in patients without cancer and cannot be used primarily to prevent malformations as birth defects multifactorial and unpredictable. Additionally, chemotherapy may lead to lower ovarian reserve in patients, reducing the number of oocytes retrieved and subsequent embryos for transfer. In these cases, PGT-A may not be recommended given the risk of not having any embryo to transfer. We recently published data demonstrating that patients with less than four 2pn zygotes have a 9.5-fold increased risk of having zero blastocysts and a 2.6-fold increased risk of having zero biopsy-quality blastocysts compared to patients that had at least four 2pn zygotes [23]. In addition, normal babies have been reported after transfer of embryos deemed abnormal on PGT-A testing [24].

The patient in case 1 was treated with a GnRH agonist before oocyte retrieval during her chemotherapy. It is hypothesized that GnRH agonists are chemoprotective in that they suppress the hypothalamic–pituitary–gonadal axis, putting the ovary in a more dormant state. This may lead to reduced damage from chemotherapeutic agents, but this mechanism is not fully understood [5]. The protective effects of such agents have best been studied in the context of breast cancer. In one study examining GnRH agonists, ovarian failure was defined as the absence of menses 2 years after treatment. The ovarian failure rate was 22% in the chemotherapy-alone group and 8% in the group treated with a GnRH agonist alongside their chemotherapy. The group receiving GnRH agonist also had a significantly higher pregnancy rate [25]. A meta-analysis also demonstrated higher pregnancy rates in premenopausal women with early breast cancer who were treated with GnRH agonists in conjunction with their chemotherapy compared to those who did not receive GnRH agonist therapy [26]. Given this data, GnRH agonist use during chemotherapy should be considered for breast cancer patients, especially those who must undergo treatment prior to fertility preservation. This treatment may help improve the number of oocytes retrieved, which increases pregnancy and live birth rates, but is also important if patients are considering PGT-A, as discussed above.

The largest study investigating fertility preservation soon after chemotherapy reported oocyte retrieval outcomes for patients with a diagnosis of cancer or another medical illness requiring gonadotoxic chemotherapy but did not include outcomes of embryo transfer cycles. The authors report on 11 patients who received chemotherapy within 6 months of ovarian hyperstimulation. They found lower antral follicles counts and higher cycle cancellation rates in patients exposed to chemotherapy before IVF compared to those with no chemotherapy exposure. However, for patients who ultimately underwent oocyte retrieval, there was no difference in total number of oocytes or mature oocytes retrieved [27]. The study is limited in that most patients who had chemotherapy exposure before retrieval had a hematologic cancer while those who were undergoing fertility preservation before chemotherapy had breast cancer. Additionally, outcomes were not subdivided based on type of chemotherapeutic agents that patients were exposed to. While these authors showed a similar number of oocytes retrieved in patients undergoing retrieval shortly after chemotherapy, other studies have found that cancer survivors undergoing IVF many years after chemotherapy have fewer oocytes retrieved and embryos available, as well as lower pregnancy and live birth rates [28].

Given the limited data on fertility outcomes resulting from oocytes or embryos preserved after chemotherapy exposure, it is imperative to monitor the outcomes of all cancer patients who undergo IVF soon after chemotherapy (<6-12 months), specifically the rates of miscarriage and birth defects. We would like to see a national database developed to track outcomes for these patients. These two cases add valuable information and are the first of their kind to report on embryo transfer outcomes using embryos preserved after chemotherapy exposure in the setting of breast cancer.

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