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Oocyte Donation Treats Infertility in Survivors of Malignancies: Ten-Year Experience¹

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INTRODUCTION

Increasing numbers of women achieve long-term survival following the diagnosis of cancer. Improvements in chemo- and radiotherapy have altered the clinical course and outcome of many malignancies once considered terminal. For instance, advances in the treatment of all stages of Hodgkin's disease have resulted in long-term survival in more than 70% of patients (1). The number of survivors of childhood or

adolescent cancer is substantial and rising as contemporary techniques for treating disease improve. As a result, many women of reproductive age are now able to conceive spontaneously and carry pregnancies despite their prior diagnosis. However, in other cases, following cancer treatment, ovarian function may be lost or compromised, and reliance on assisted reproductive techniques is required. These women are able to achieve pregnancy through oocyte donation.

Missing from most reports is the follow-up of women treated with assisted reproductive techniques. We report the result of 10-year work with cancer patients attempting oocyte donation for treatment of their infertility. Included are reproductive, neonatal, and medical follow-up experiences.

MATERIALS AND METHODS

The method of oocyte and embryo donation has previously been described (2). Protocols used were reviewed and approved by both the Institutional Review Board (IRB) of the California Medical Center, Los Angeles, CA (1987–1995), and the IRB of Columbia-Presbyterian Medical Center, New York, NY (1995–1997). Oocyte donors and recipients were screened medically, reproductively, and psychologically. Donors received gonadotropin releasing hormone agonist (GnRH-a) to produce a castrate state and ovarian hyperstimulation with menotropins. Oocytes were retrieved transvaginally by ultrasound-guided needle aspiration and fertilized in vitro. Embryos were transferred at 48 or 72 h postaspiration.

Recipients received a combination of sequentially administered estrogen and progesterone to prepare the uterus for embryo transfer (3). Prior to initiating the actual attempt at oocyte donation, endometrial biopsies documented a progesterational lining during a mock cycle in which samples were taken on day 21 of hormone replacement.

Oncologists were consulted prior to initiating therapy. A second opinion was also obtained from an independent oncologist, in addition to the patient's primary care provider. Additional opinions were felt to be particularly important for cases where disease states were known to be in remission, but not cured. All patients were believed by oncologists to be disease free, and without significant risk of recurrence.

Psychiatric Consultation was also required. Evaluation of the patient's emotional and psychosocial supports was considered mandatory. Patients commonly

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Table I. Outcome Data for Women ($n = 24$) Enrolled in Oocyte Donation from 1989 Through 1997

Recipient age (years)	42.7 $\pm$ 6.1 years (range 28–53 years)
Number of cycles performed	40 (range 1–4 per recipient)
Embryos per ET	4.1 $\pm$ 1.0 (range 2–6)
Clinical pregnancies	17/40 (42.5%)
Spontaneous abortions	2/17 (11.8%)
Delivery rate per ET	37.5% (15/40)
Singletons	10
Twins	5
Obstetric Outcomes	
Cesarean section	10 (66%)
Placenta Accreta	2
Neonatal complications	0
Recurrent maternal disease after delivery	1

related considerable anxiety regarding their own health and survival, and also that of their future child.

RESULTS

Between 1989 and 1997, 24 women were evaluated, cleared for treatment, and received an embryo transfer. Their cancers included breast ($n = 5$), Hodgkins lymphoma ($n = 5$), ovarian ($n = 4$), non-Hodgkins lymphoma ($n = 3$), sarcoma ($n = 2$), cervical ($n = 2$), thyroid ($n = 2$), and colon ($n = 1$). The demographic profile, cycle outcome, and obstetrical performance data for these women are presented in Table I. All delivered babies are alive and well. Following delivery, patients were followed for a minimum of 3 years and a maximum of 13 years. All mothers but one remain disease free. This patient experienced a recurrence of her Hodgkin's lymphoma 5 years after delivery. She received remedial chemotherapy and remains healthy, actively raising her 13-year-old son.

Two women were not enrolled because of an inability to adequately respond to hormone replacement therapy. Both patients had received pelvic radiation—one for treatment of a pelvic lymphoma, the other as a result of an ovarian dysgerminoma. Despite large doses of daily estradiol (10 mg/day), a fibrotic, atrophic endometrium persisted in both patients.

DISCUSSION

Although difficult to estimate, it is believed that as many as 2600 young adults are diagnosed with cancer

each year (4). Many of these cancers have reasonable survival rates. Reproductive difficulties experienced in survivors are many times secondary to the oncologic treatments rendered to cure disease. Radiation therapy leads to an oophoritis that may harm or even destroy germ cells. This is particularly apparent with increased dose and duration of therapy (5). Pelvic radiotherapy above a dose of 10 Grays (Gys) induces permanent ovarian insufficiency. Radiation may also lead to extensive and permanent damage to the endometrium and myometrium. Understanding the potential damage to the endometrium, an endometrial biopsy during a mock cycle was required of all women who received previous radiation treatment. Endometrial fibrosis and atrophy precludes attempts at restoring a receptive environment for embryo implantation. This can best be ascertained by endometrial biopsy after several months of estrogen priming. Radiotherapy is most often used in women with lymphomas, leukemias, and pelvic tumors such as dysgerminomas and sarcomas, all of which occur in younger women.

Chemotherapy also contributes to ovarian failure. Certain agents may be germ cell toxic even if endocrinologic function remains intact. The most devastating effects are seen with alkylating agents, where often women posttreatment experience hypergonadotropic hypogonadism. Women of reproductive age receiving cytotoxic therapy commonly experience some degree of ovarian failure. Their ovaries lose function either because of injury to the oocytes or through loss of their supporting cells within the follicle. Eventually, endocrinologic and reproductive function ceases.

In women receiving both pelvic radiation and chemotherapy, the potential for ovarian failure is greatest. A reduction in the number of ova and primordial follicles together with stromal fibrohyalinization is evident in histologic sections of women undergoing combined treatment. Subsequent recovery of function is rare. Younger women who possess a greater complement of oocytes at the time of treatment are more likely to retain function. A return of normal menstrual cyclicity usually precedes pregnancy in those maintaining fertility potential. Menopausal symptoms or prolonged amenorrhea typically denotes sterility.

The long- and short-term teratogenic effects of cancer therapy on children born to women who have previously undergone chemotherapy or radiotherapy are largely unknown. Damage to the gamete resulting in

genetic mutations may occur after either form of therapy. In general, pregnancy after chemotherapy has not been reported to result in increased rates of fetal wastage or malformations. However, there are reports of increased malformations following combined chemo–radiotherapy (6).

There has been a previously noted increase in the spontaneous abortion rate of women successfully conceiving following oocyte donation in whom multiple agent chemotherapy had been administered (7). The reason for this observation remains elusive, but may represent a persistent effect of the drugs on the basalis from which the endometrial lining is generated. Interestingly, following miscarriage, if patients remain persistent in their attempts, most conceive again and deliver normally. The cumulative birth rates of oncology patients and the life-table analysis of cycles of oocyte donation in cancer patients remain the same as others with different diagnoses (8).

Careful preconceptual screening, counseling, and patient selection is critical to the successful outcome of the recipients of donor oocytes. This is especially true for patients previously diagnosed and treated for malignancies. Thorough medical, surgical, psychologic, obstetric, and family histories are necessary to assist in guiding evaluations. Screening is directed at identifying conditions that negatively impact upon pregnancy, or perhaps contraindicate any attempt at conception.

SUMMARY AND CONCLUSIONS

Women who are survivors of malignancy may achieve pregnancy through oocyte donation. The largest obstacle to successful reproduction in cancer patients relates to iatrogenic damage to the primary reproductive organs associated with their primary oncology treatment. Reactive damage from surgery, radiation, or chemotherapy may render these organs

nonfunctional and irreparable. In cases where the ovary is primarily affected, oocyte donation provides a logical alternative for childbearing.

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