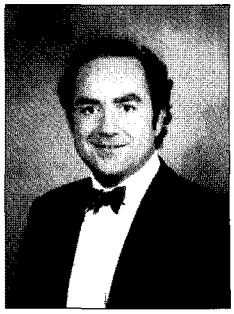
S 29

Kutluk Oktay

Tenure Track Associate Professor
Cornell University Weill Medical College
Center for Reproductive Medicine & Infertility



2005-present	Director Program for Fertility Preservation Research Division of Reproductive Medicine & Infertility, Weill Medical College of Cornell University
2003-present	Associate Professor of Reproductive Medicine, Tenure Track Division of Reproductive Medicine & Infertility, Weill Medical College of Cornell University
2003-present	Associate Professor of Obstetrics & Gynecology, Tenure Track Division of Obstetrics & Gynecology, Weill Medical College of Cornell University
2000-2003	Director Division of Reproductive Endocrinology, Brooklyn Hospital
2000-2003	Assistant Professor of Reproductive Medicine, Center for Reproductive Medicine & Infertility, Weill Medical College of Cornell University
1996-2000	Director Division of Reproductive Endocrinology, New York Methodist Hospital
1997-2003	Assistant Professor of Obstetrics & Gynecology, Department of Obstetrics & Gynecology, Weill Medical College of Cornell University, New York, NY
1996-1997	Assistant Professor Department of Obstetrics & Gynecology, State University of New York at Brooklyn Brooklyn, NY
1995-1996	Senior Registrar Assisted Conception Unit, Leeds General Infirmary, University of Leeds, School of Medicine, Leeds, UK
1995-1996	ACOG-RCOG Exchange Fellow Department of Obstetrics & Gynecology, University of Leeds, School of Medicine Leeds, UK
1995-1996	FELLOWSHIPS ACOG-RCOG (WellBeing) UK Research Fellowship, University of Leeds School of Medicine, Division of Reproductive Biology, Dept. Obstetrics & Gynecology

1993-1995	Assistant Instructor
	Department of Obstetrics & Gynecology, The University of Texas at San Antonio, San Antonio, Texas
1993-1995	FELLOWSHIPS
	Reproductive Endocrinology & Infertility, University of Texas HSC at San Antonio
1992-1993	Chief Resident and Instructor Department of Obstetrics & Gynecology, University of Connecticut Health Center, Farmington, Connecticut
1991-1993	RESIDENCIES
	Obstetrics & Gynecology, University of Connecticut Health Center
1989-1991	RESIDENCIES
	Obstetrics & Gynecology, Columbia University College of Physicians & Surgeons, Harlem Hospital Center, NY
1988-1989	RESIDENCIES
	Internal Medicine, Cook County Hospital, Chicago
1986-1988	RESIDENCIES
	Internal Medicine, Marmara University Hospital, Istanbul
1980-1986	M.D. DEGREE
	Hacettepe University Medical School, Ankara, Turkey

Cryopreservation and Germ Stem Cells: What Is the Connection?

Kutluk Oktay

Cornell University Weill Medical College

There are over 75,000 women sterilized as a result of chemotherapy and radiotherapy in the U.S. alone. Tens of thousands of women are sterilized due to surgery performed for gynecological cancer. It is against this backdrop that there is an increased demand for new assisted reproductive technologies to preserve fertility.

When patients have at least 3-4 weeks prior to treatment, and if there is no contraindication for ovarian stimulation, *in vitro* fertilization and embryo cryopreservation can be used to preserve fertility.

However, in the case of an estrogen-dependent cancer (i.e. breast cancer) ovarian stimulation with conventional regimens is contraindicated. In that instance, tamoxifen can be used for ovarian stimulation, *in vitro* fertilization, and embryo cryopreservation. With tamoxifen, embryo yield can be increased by 2-6 folds compared to natural cycle-IVF, where no simulation is performed. In the case of endometrial cancer, tamoxifen cannot be used because of its stimulatory effect on endometrium. In which instance, aromatase inhibitors can be used for ovarian stimulation. Recent work has shown that aromatase inhibitor drugs can induce multiple ovarian follicle development and result in pregnancy rates comparable to other oral ovulation induction agents. Yet they can completely block estrogen production during ovarian stimulation and thus will not stimulate estrogen-dependent cancer.

When the patient is single and does not want to use donor sperm, another strategy is to cryopreserve unfertilized oocytes. However, the pregnancy rates from frozen-thawed oocytes have historically been lower than that of obtained from frozen-thawed embryos.

When feasible, we encourage our patients to cryopreserve embryos rather than oocytes.

Recent reports on the other hand, showed improved success rates with oocyte freezing, and in the future, oocyte freezing may become equally acceptable.

In many cases, there is not enough time to perform an ovarian stimulation prior to cancer treatment. In that case, we perform ovarian cryopreservation for later auto-transplantation. We have performed 6 cases of ovarian transplantation, which resulted in ovarian function for as long as nearly 6 years. The most practical approach for ovarian transplantation is grafting of ovarian cortical pieces underneath the forearm or abdominal skin. With this approach, ovarian tissue can be closely monitored, tissue can be inserted and removed under local anesthesia, and oocytes can be collected percutaneously for *in vitro* fertilization. Until now, embryo development and live birth were achieved in two patients. Ovarian transplantation can not only preserve fertility but also reverse menopause, and this may be an added benefit for some.

Finally, recent evidence suggested that ovarian primordial follicle can be renewed in postnatal mammals. Our labs generated some evidence in support of this hypothesis in humans.

In conclusion, there is a multitude of options for fertility preservation; to make the best use of these options these patients should be referred to an assisted reproduction center as soon after the diagnosis as possible. For those who have not been able to preserve fertility and who have undergone ovarian failure as a result of cancer treatments however, oocyte donation and surrogacy may be the final resort.

References

Oktay K, Buyuk E, Rosenwaks Z, Rucinski J. A technique for transplantation of ovarian cortical strips to the forearm. Fertil Steril. In Press.

Oktay K, Buyuk E, Davis O, Yermakova I, Veeck L, Rosenwaks Z. Fertility preservation in breast cancer patients: *In vitro* fertilization and embryo cryopreservation after ovarian stimulation with tamoxifen. Human Reprod 2003;18(1):90-95.

Oktay K. Evidence for limiting ovarian tissue harvesting for the purpose of ovarian transplantation to women younger than 40 years of age. J Clin Endocrinol Metab 2002 Apr;87(4):1907-8.

Oktay K. Ovarian cryopreservation and transplantation: Preliminary findings and implications for cancer patients. Hum Reprod Update, 7:526-534, 2001.

Oktay K., Economos K, Rucinski J, Kan M, Veeck L, Rosenwaks Z. Endocrine function and oocyte retrieval after autologous transplantation of ovarian cortical pieces to the forearm. JAMA, 286:1490-1493,2001.

Oktay K, Karlikaya G, Aydin B. A technique for laparoscopic transplantation of frozen-banked ovarian tissue. Fertil Steril, 75:1212-1216, 2001.

Oktay K and Karlikaya G. Ovarian function after autologous transplantation of frozen-banked human ovarian tissue. N Engl J Med, 342:1919, 2000.

Oktay K, Newton H, Gosden RG. Transplantation of cryopreserved human ovarian tissue results in follicle growth in SCID mice. Fertil Steril, 73:599-603, 2000.

Oktay K, Newton H, Mullan J and Gosden R. Development of human primordial follicles to antral stages in SCID/hpg mice stimulated with follicle stimulating hormone. Human Reprod., 13:1133-1138, 1998.

Oktay K, Briggs D and Gosden RG. Ontogeny of FSH receptor gene expression in isolated human ovarian follicles. J Clin Endoc Metabol. 82:3748-3751, 1997.

Oktay K, Nugent D, Newton H, Salha O, Chattergee P and Gosden R. Isolation and characterization of primordial follicles from fresh and cryopreserved human ovarian tissue. Fertil Steril, 67:481-486,1997.

Oktay K & Buyuk E. The technique of ovarian transplantation: Laboratory and clinical aspects. In: A color atlas for human assisted reproduction: Laboratory & clinical insights. Patrizio P, Guelman V, Tucker M (eds). Lippincot, 2003;229-240.

Oktay K, Kan M, Rosenwaks Z. Recent progress in oocyte and ovarian tissue cryopreservation. Curr Opin Obstet Gynecol, 13:263-268, 2001.

Oktay K. Ovarian Cryopreservation and Transplantation. In: Textbook of Assisted Reproductive Technology and Clinical Perspectives. Gardner DK, Weissman A, Howles CM, Shoham Z (eds). Martin Dunitz Limited. London, UK:2001; 279-284.

Oktay K. Spontaneous pregnancies and live birth after heterotopic transplantation of frozen-thawed ovarian tissue. Human Reproduction, Feb 2006 (e-print ahead of publication).

Johnson J, Canning J, Kaneko T, Pru JK, Yilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary, Nature, 2004 Mar 11; 428(6979): 145-50.

Johnson J, Bagley J, Skaznik-Wikiel M, Lee HJ, Adams GB, Niikura Y, Tschudy KS, Tilly JC, Cortes ML, Forkert R, SpitzerT, Iacomini J, Scadden DT, Tilly JL. Cell, 2005 Jul 29; 122(2): 303-15.

Johnson J, Skaznik-Wikiel M, Lee HJ, Niikura Y, Tilly JC, Tilly JL. Setting the record straight on data supporting postnatal oogenesis in female mammals. Cell Cycle, 2005 Nov; 4(11): 1471-7.