Current approach to fertility preservation by embryo cryopreservation

Giuliano Bedoschi, M.D.,[a,b] and Kutluk Oktay, M.D.[a,b]

[a] Laboratory of Molecular Reproduction and Fertility Preservation, Obstetrics and Gynecology, New York Medical College, Valhalla; and [b] Innovation Institute for Fertility Preservation and In Vitro Fertilization, New York, New York

The ovaries are susceptible to damage following treatment with gonadotoxic chemotherapy, pelvic radiotherapy, and/or ovarian surgery. Gonadotoxic treatments have also been used in patients with various nonmalignant systemic diseases. Any women of reproductive age with a sufficiently high risk of developing future ovarian failure due to those medical interventions may benefit from embryo cryopreservation though the tools of assessment of such a risk are still not very precise. Furthermore, the risk assessment can be influenced by many other factors such as the delay expected after chemotherapy and the number of children desired in the future. Embryo cryopreservation is an established and most successful method of fertility preservation when there is sufficient time available to perform ovarian stimulation. This publication will review the current state, approach, and indications of embryo cryopreservation for fertility preservation. (Fertil Steril® 2013;99: 1496–502. ©2013 by American Society for Reproductive Medicine.)

Key Words: Embryo cryopreservation, fertility preservation, ovarian damage

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/bedoschig-fertility-preservation-embryo-cryopreservation/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

In the U.S., the estimated number of new cases of invasive cancer expected among women in the year 2012 is 790,740 (1). Early detection and improvements in screening have increased the number of premenopausal women diagnosed with cancer. As a result, it is estimated that a malignancy will be diagnosed in one among 46 females under the age of 40 years. Based on the cancer diagnosis, we have estimated that approximately half of these females will receive a form of gonadotoxic treatment hence approximately 1% of females with reproductive potential are at risk. With recent advances in cancer therapy, many of these patients will be cured by combination treatment with chemotherapy, radiotherapy, and/or surgery (2). In fact, during the most recent 5 years for which there are data (2004–2008), cancer death rates in women decreased by more than 1.6 % per year (1). However, these treatments have also long-term sequelae and patients must be informed of the possible risks of developing premature ovarian failure and infertility.

As the existing literature based on surveys (3) as well as qualitative and exploratory studies have revealed, fertility is a clear issue for cancer patients (4). Fertility preservation education is not only needed for those involved in reproductive health. Despite the fact that affected patients and their families are interested in information about fertility issues, only a few receive information prior to treatment for different reasons (Fig. 1) (5). Therefore, it is important for cancer care professionals to be familiar with the current techniques for fertility preservation in women with cancer.

Fertility preservation is not limited to cancer patients. Similar to cancer, there are some non-oncological systemic diseases which are treated with chemotherapy or radiotherapy, such as autoimmune and hematological conditions (6). In addition, there are other interventions that may impair fertility, such as recurrent ovarian surgery for benign disease or prophylactic oophorectomy in women with *BRCA* mutations. Therefore, fertility preservation is also commonly utilized in non-cancer conditions, increasing the number of females who benefit from this discipline even further.

The available fertility preservation methods range from established techniques such as embryo and oocyte cryopreservation to experimental techniques such as ovarian tissue

Received January 15, 2013; revised March 6, 2013; accepted March 7, 2013; published online March 25, 2013.

G.B. has nothing to disclose. K.O. has nothing to disclose.

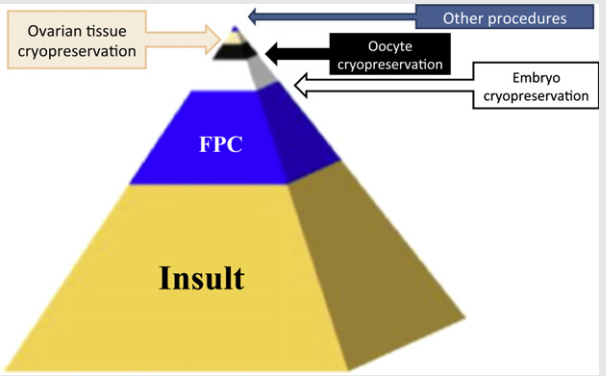
Supported in part by National Institute of Child Health and Human Development grants R01 HD053112 and R21 HD061259.

Reprint requests: Kutluk Oktay, M.D., Laboratory of Molecular Reproduction and Fertility Preservation, Obstetrics and Gynecology, 40 Sunshine Cottage Road, Valhalla, New York 10595 (E-mail: koktay@fertilitypreservation.org).

Fertility and Sterility® Vol. 99, No. 6, May 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.03.020

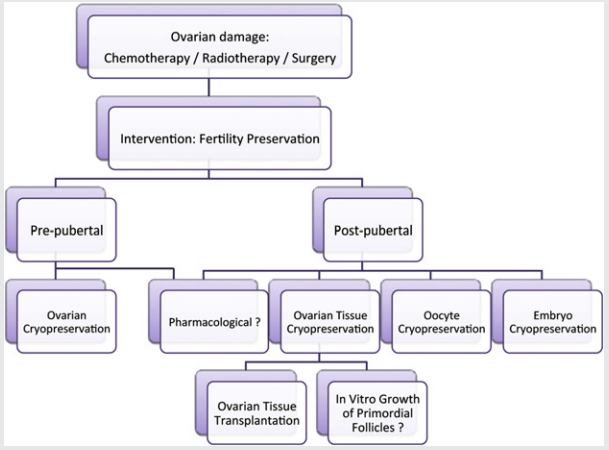
FIGURE 1



"Pyramid" of fertility preservation. Medical interventions including chemotherapy, radiotherapy, and surgery act as insults to ovarian reserve and may result in premature ovarian failure and infertility. However, of all the patients at risk for premature ovarian failure, only a fraction will be referred to fertility preservation consultation (FPC) (5). Of those even a smaller fraction will be undergoing fertility preservation due to social, economic, or technical hurdles. Of all techniques offered, embryo cryopreservation is most commonly used, followed by oocyte cryopreservation, ovarian tissue freezing, and other methods, in that order.

Bedoschi. Fertility preservation by embryo cryopreservation. Fertil Steril 2013.

FIGURE 2



A simplified scheme for fertility preservation options. In pre-pubertal girls, ovarian cryopreservation may be the only practical option. In post-pubertal females, a wider range of options is available with embryo cryopreservation being the most established method for patients with a male partner or who wish to use donor sperm. Oocyte cryopreservation, now considered an established method of fertility preservation by the American Society for Reproductive Medicine (7), is an option for older post-pubertal female children and single women. In cases where there is insufficient time for ovarian stimulation, ovarian cryopreservation as well as immature oocyte retrieval for in vitro maturation (followed by oocyte or embryo cryopreservation) may also be considered. In vitro growth (IVG) of isolated immature follicles is a theoretical option that may offer advantages in the future for females who have undergone ovarian freezing when there is a risk of ovarian involvement with cancer. The simplest approach to fertility preservation could have been a pharmacological intervention; however there is no proven hormonal treatment to preserve fertility. In the future, with the discovery of the mechanisms responsible for the chemotherapy-induced damage to the primordial follicles (8, 66), targeted pharmacological methods may be developed.

Bedoschi. Fertility preservation by embryo cryopreservation. Fertil Steril 2013.

cryopreservation (Fig. 2) (7, 8, 66). This publication will review the current state, approach, and indications of embryo freezing for fertility preservation.

EMBRYO CRYOPRESERVATION FOR FERTILITY PRESERVATION

Embryo cryopreservation is an established technique that has been proven to be safe and effective in couples undergoing in vitro fertilization (IVF) treatment. Since the introduction of this technique in assisted reproductive technology (ART) (9), it became apparent that it also held a potential for fertility preservation purposes (10, 11). The first case of embryo cryopreservation for fertility preservation took place in 1996, with the application of a natural IVF cycle prior to chemotherapy in a woman diagnosed with breast cancer (12). Since then, embryo cryopreservation has become the most established technique for fertility preservation.

The procedure can be offered to women in reproductive age with available partner or for women using donor semen. Standard protocols for ovarian stimulation and oocyte retrieval usually requires 2 to 6 weeks of time commitment, depending on where in the menstrual cycle the patient presents.

Special considerations should be given to ovarian stimulation for fertility preservation patients. Ovarian stimulation protocols using gonadotropin-releasing hormone (GnRH) antagonists should be preferred, as they are associated with a lower risk of ovarian hyperstimulation syndrome (OHSS) (13). The risk of OHSS can further be decreased by triggering final oocyte maturation by GnRH agonists (14, 15) and in our center, this is the routine approach we take for cancer patients. Furthermore, to our experience, the use of GnRH agonists can also speed the interval from oocyte retrieval to next menses as well as reducing the likelihood and extent of residual ovarian cyst formation. This in turn improves the chances of multiple back-to-back cycles before initiating cancer treatment (16). In many instances there may not be sufficient time to wait for the menses to begin before initiating ovarian stimulation and random start protocols can be used with good results (17, 18). Patients with hormone sensitive tumors can also benefit from specific protocols that reduce estrogen exposure (16, 19–21).

Alternatively, immature oocytes can be harvested in an unstimulated cycle and fertilized following in vitro maturation (IVM) though the effectiveness of this approach in comparison to embryo freezing with mature oocytes remains to be determined. On the other hand, since a fraction of oocytes retrieved during IVF are immature and typically discarded, these germinal vesicle oocytes can be subjected to IVM to increase the oocyte and embryo yield in fertility preservation cycles (22).

SUCCESS RATES

As an established technique embryo, cryopreservation has reliable success rates. Even though pregnancy rates with