Should Ovarian Tissue Cryopreservation Be Recommended for Cancer Patients?¹

Joseph G. Schenker^{2,3} and Mohammad Fatum²

The emergence of ovarian tissue cryopreservation (OTCP) for fertility conservation has led to a new worldwide trend of ovarian tissue banking for reproductive cancer patients, scheduled to undergo chemotherapy or radiotherapy (1). Since the survival of young women and children who undergo such curative anti-cancer treatment is increasing, it is imperative for the consulting clinician to have an updated and accurate understanding of the proven benefits and the limitations of this new and hitherto evolving technique. OTCP was shown to be successful in several animal models during the last decades. In 1960, Parrott reported successful pregnancies in mice after implantation of frozen-thawed ovarian grafts (2). Other studies reproduced the similar results in mice (3) and in sheep (4). Despite these promising preliminary animal outcome, the efficiency of ovarian tissue autografting whether orthotopic (the autotransplantation to the ovarian pedicle) or heterotopic (the autotransplantation to a different site) has not yet been clearly demonstrated in humans (5,6).

Since the primordial and primary follicles can survive the freezing–thawing procedures, it was hoped that in vitro maturation would be an important source for harvesting mature oocytes (7,8). However, the in vitro maturation of both animal and human follicles was no less disappointing than autografting. There still are no reports of harvesting mature oocytes from in vitro culturing and maturation of primordial and primary follicles. Hence, there is increasing interest in improving the cryopreservation, autografting, and the in vitro culturing and maturation techniques, ne-

cessitating further intensive research to increase their efficiency and to test their safety (9). To our knowledge, no pregnancy or embryo transfer was reported in humans as a result of utilizing cryopreserved ovarian tissue.

From the aforementioned data, it seems that the use of ovarian tissue banking as a method to preserve fertility in cancer-treated-female patients is still in its early stages. We believe that at this stage of experience and outcome, OTCP should not be proposed to these patients. These relatively debilitated cancer patients are a priori in a suboptimal health state and hence, the risk of invasive surgical procedures for retrieving ovarian tissue is not justified.

Women should be informed of the current state of data concerning the success rates in order to prevent developing false expectations and further disappointments.

Furthermore, ovarian transplantation might be unsafe in some malignancies (e.g. acute leukemia) because of the risk of ovarian involvement and the possible receding of malignant cells through the implant (10,11). On the other hand, studies have shown that ovarian tissue harvested before high dose chemotherapy for lymphomas may not carry a risk of disease transmission by autotransplantation (12,13). However, even in these low risk cases, transmission of the malignant cells is difficult to exclude completely. Thus, if autografting is considered, testing for malignant cells in the tissue must be performed using adequate techniques. This subject needs further extensive research.

Animal models show that ovarian slices can convey short time function only. Assuming that these studies apply to human ovarian tissue, the potential of achieving pregnancy is limited. For this reason it is recommended to transplant the auto-graft only when immediate fertility is desired (11).

Studies on organ cryopreservation, ovarian freezing, and transplantation are in its first steps of research

¹As of the date this paper was submitted, Donnez et al. (Lancet, Oct. 2004) reported a live birth after orthotopic transplantation of cryopreserved ovarian tissue.

²Department of Obstetrics and Gynecology, Hadassah, Hebrew University Hospital, Ein kerem, Jerusalem, Israel.

³To whom correspondence should be addressed at The Department of Obstetrics and Gynecology, Hadassah University Hospital, Ein Kerem, P.O. box 12000, Jerusalem 91120, Israel; e-mail: schenker@cc.huji.ac.il.

and thus it is not an applicable modality and cannot be recommended as a fertility-conserving measure in the near future. Since OTCP is yet to be yielding and in the absence of other more promising modalities, we believe that in order to preserve potential fertility in cancer patients, they should be advised to undergo one cycle of ovarian super-ovulation with subsequent IVF before chemotherapy or irradiation in order to obtain embryos for cryopreservation. This strategy can be suggested to stable couples, since fertilization can be performed with the partner's sperm.

These frozen zygotes have an acceptable rate of viability and so far are the only proven modality ensuring delayed pregnancy. To our experience one cycle of ovarian super-ovulation knowledge, is adequately safe and is equally acceptable by these patients and their consulting oncologists in most malignancies without any significant deleterious influence of the delay in chemotherapy/radiotherapy on patients' prognosis.

In single adolescent women, donor sperm can be used for oocyte fertilization. In accordance with their desires, both couples and single women will always have embryo transfer as an option. According to the present state, embryos can be cryopreserved for 5 years and in some countries according to legislation or regulation, even to 10 years, then women can decide whether they are interested in the sustained cryopreservation and transfer of these embryos.

With patients refusing to use donor sperm due to ethical or religious attitudes, oocyte harvesting and freezing might be offered despite present low fertilization and pregnancy rates. This modality is still in its early experimental stages and only few cases of pregnancies were achieved, however it is still more promising than OTCP in which no cases of pregnancies were reported.

Until large-scale human transplantation studies to test and improve the efficacy and the safety of OTCP procedure are undertaken, this procedure should not be recommended as a routine therapeutic approach. The current experience with no documented pregnancy in humans from OTCP, does not justify exposing these patients to the risks of anesthesia and invasive surgical procedure before the definitive anti-cancer treatment. This is of utmost importance in order to avoid creating false expectations and disappointments in these patients. Therefore, these women should be recommended to undergo one cycle of ovarian super-ovulation with subsequent IVF with partners sperm in coupled women and donor sperm

in single women in order to achieve embryos for cryopreservation.

However, only in prepubertal girls in whom ovulation induction can not be performed and mature oocytes can not be achieved, OTCP is at present the only option. These patients and parents ought to be informed that this clinical approach is still in its early stages of experimentation and their chance to preserve fertility can not be guaranteed.

REFERENCES

1. Meirow D, Fasouliotis SJ, Nugent D, Schenker JG, Gosden RG, Rutherford AJ: A laparoscopic technique for obtaining ovarian cortical biopsy specimens for fertility conservation in patients with cancer. *Fertil Steril* 1999; May;71(5):948-951
2. Parrott DM: The fertility of mice with orthotopic ovarian grafts derived from frozen tissue. *J Reprod Fertil* 1960;1:230-241
3. Carroll J, Gosden RG: Transplantation of frozen-thawed mouse primordial follicles. *Hum Reprod* 1993;8:1163-1167
4. Gosden RG, Baird DT, Wade JC, Webb R: Restoration of fertility to oophorectomized sheep by ovarian auto-grafts stored at -196 C. *Hum Reprod* 1994;9:597-603
5. Radford JA, Lieberman BA, Brison DR, Smith ARB, Russel SA, Watson AJ, Clayton JA, Harris M, Gosden RG, Shalet SM: Orthotopic reimplantation of cryopreserved ovarian cortical strips after high-dose chemotherapy for Hodgkin's lymphoma. *Lancet* 2001;357:1172-1175
6. Oktay K, Karlikaya G: Ovarian function after transplantation of frozen, banked autologous ovarian tissue [letter]. *N Engl J Med* 2000;342:1919
7. Hovatta O, Silve R, Krausz T, Abir R, Margara R, Trew G, Lass A, Winston RM: Cryopreservation of human ovarian tissue using dimethylsulphoxide and propanediol-sucrose as cryoprotectants. *Hum Reprod* 1996;11:1268-1272
8. Oktay K, Nugent D, Newton H, Salha O, Chatterjee P, Gosden RG: Isolation and characterization of primordial follicles from fresh and cryopreserved human ovarian tissue. *Fertil Steril* 1997;67:481-486
9. Picton HM, Gosden RG: In vitro growth of human primordial follicles from frozen-banked ovarian tissue. *Mol Cell Endocrinol* 2000;166:27-35
10. Shaw JM, Bowles J, Koopman P, Wood EC, Trounson AO: Fresh and cryopreserved ovarian tissue samples from donors with lymphoma transmit the cancer to graft recipients. *Hum Reprod* 1996;11:1668-1673
11. Oktay K: Ovarian tissue cryopreservation and transplantation: Preliminary findings and implications for cancer patients. *Hum Reprod Update* 2001;7:526-534
12. Kim SS, Radford J, Harris M, Varley J, Rutherford AJ, Lieberman B, Shalet S, Gosden R: Ovarian tissue harvested from lymphoma patients to preserve fertility may be safe for autotransplantation. *Hum Reprod* 2001;10:2056-2060
13. Meirow D, Ben Yehuda D, Prus D, Poliack A, Schenker JG, Rachmilewitz EA, Lewin A: Ovarian tissue banking in patients with Hodgkin's disease: Is it safe? *Fertil Steril* 1998; Jun;69(6):996-998