Review Article

Fertility preservation for ovarian or uterine cancer patients with reference to assisted reproduction technology

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ABSTRACT

Fertility preservation has been paid much attention recently, as the survival rate of cancer patients after therapy has increased significantly. Cryopreservation of gametes or embryos has been practiced prior to cancer therapy, to preserve fertility, as various modes of cancer therapy are gonadotoxic, reducing reproductive potential of cancer survivors. Although cryopreserving semen or testicular tissue has been the prominent means of fertility preservation for men, it has been still experimental for pre-pubertal boys. Treating by Assisted reproduction Techniques with cryopreservation of oocytes or embryos is the promising way of fertility preservation in women prior to cancer therapy. Livebirths have been reported after auto transplantation of cryopreserved ovarian cortex. Such an approach may not be practical in women with ovarian or endometrial or Estrogen sensitive breast cancer as transplantation of ovarian cortex may reintroduce the disease. Oophorectomy in such patients is not uncommon leading to total infertility of patients. Alternative approaches are available to preserve fertility of such women. Harvesting oocytes for cryopreservation in women without male partners or embryos after in vitro maturation and ICSI of harvested oocytes in women with male partners have been reported as modern means of fertility preservation in ovarian cancer patients. Efficacy of such approaches is reviewed in this article.

Keywords: Fertility preservation, IVM, ovarian cancer, uterine cancer

INTRODUCTION

Treating cancer has been the greatest challenge of medical fraternity for so many decades. One in every 250 adult is predicted to be a childhood cancer survivor in this decade (Blatt, 1999).[1] Advances made in chemo/radio therapy have increased the lifespan of cancer survivors. Chemo and radiotherapy leads to gonadal dysfunction in men and women (Howell and Shalet, 1998)[2] leading to reduced fertility potential of cancer survivors in reproductive age. The chemo and radiotherapy agents are gonadotoxic and result in premature failure of reproductive function. Dose of chemotherapy agent and age of patient influence the extent of gonadal failure (Byrne *et al*., 1992).[3] Fertility preservation, therefore, has to be planned prior to treatment of cancer.

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ROLE OF ONCOLOGISTS

Oncologists must counsel the patients prior to cancer therapy on the effect of chemotherapy or radiotherapy on fertility potential and options of fertility preservation with Assisted Reproductive Technology (Lee *et al*., 2006).[4] A survey in America showed that less than half of the oncologists refer patients to fertility preservation program (Quinn *et al*., 2009).[5] The awareness of fertility preservation among oncologists in Asia cannot be commented on now as no literature available. However, educating oncologists through public articles, continuing medical education (CME) programs, etc., is warranted at present.

FERTILITY PRESERVATION IN MEN

Cryopreservation of sperm produced through masturbation is the common mean of fertility preservation in men (Osterberg *et al*., 2014).[6] Samples may be obtained from anejaculatory men by vibratory or electro ejaculation techniques (Stahl *et al*., 2012).[7] Testicular extraction of sperm is prescribed to obtain viable sperm in azoospermic men, particularly with testicular tumors (Schrader *et al*., 2003).[8] However, such approaches are viable options in post-pubertal men. Fertility preservation by cryopreservation

of testicular tissue or *in vitro* maturation of sperm cells in pre-pubertalboys is still experimental (Stensvold *et al*., 2011).[9]

FERTILITY PRESERVATION IN WOMEN

Surgical intervention

Fertility preservation in women of reproductive age is more complicated than that of in men. Surgical interventions such as ovariopexy or ovarian transposition may help to retain the reproductive function of women with cancer if radiotherapy is the only mean of treatment (Bisharah and Tulandi, 2003).[10] Attempts were made to cryopreserve whole ovary after laparoscopic ovariectomy (Jadoul *et al*., 2007).[11] Cryopreservation of ovarian cortex prior to cancer therapy and transplantation to the patient after the disease is cured are proven to be successful with live birth (Donnez *et al*., 2004).[12] Transplantation of cryopreserved ovarian cortex from patients with advanced stage breast cancer may be safe and may not reintroduce the disease as shown in mice models (Luyckx *et al*., 2013).[13]

Controlled ovarian hyperstimulation (COH)

COH with cryopreservation of oocytes or embryos has been endorsed as the most suitable way of fertility preservation in women with cancer (American Society for Reproductive Medicine, ASRM, Committee Opinion, 2013).[14] Cryopreservation by vitrification techniques yields high survival rates for oocytes and embryos. However, to achieve successful live birth through cryopreserving oocytes or embryos, at least eight oocytes are required for patients aged <38 and more than eight oocytes in patients aged >38 (Rienzi *et al*., 2012)[15] which could be obtained by COH. COH with gonadotropins has a potential risk in estrogen-sensitive cancers and also it is time-consuming, where patients with ovarian or uterine cancer may have very short time before cancer therapy. Using aromatase inhibitors such as Letrozole for ovarian stimulation to cryopreserve embryos has been most widely accepted for cancer patients (Lee *et al*., 2006; Oktay *et al*., 2010).[4,16] Ovarian tissue cryopreservation followed by COH with agonist or antagonist to cryopreserve oocytes has been reported (Dolmans *et al*., 2014).[17] However, cryopreservation of embryos for fertility preservation requires the patients to have a male partner. In the absence of male partner, patient has to cryopreserve oocytes. COH also poses potential risks with elevated levels of estradiol in hormone-sensitive cancers (Oktay *et al*., 2010).[16]

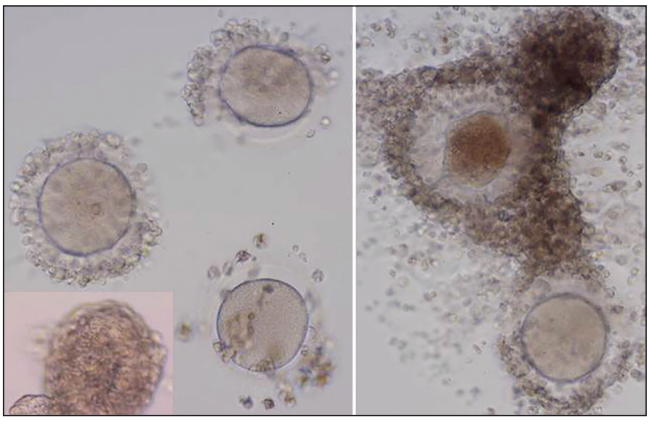

Figure 1: Immature oocytes from patient's ovary (Prasath *et al*., 2008)[25]

Fertility preservation in patients with cancer of uterus or ovaries

COH is applicable mostly in patients with cancers of non-reproductive organs. When cancer occurs in reproductive organs such as uterus or ovaries, generally, total hysterectomy with bilateral salpingo-oophorectomy is carried out. Hence, patients become totally infertile. As mentioned earlier, these patients are not recommended for COH due to shortage of time and potential risks of using gonadotropins for ovarian stimulation (Lobo *et al*., 2005).[18] Ovarian tissue cryopreservation may not be an option due to the risk of reintroducing multi-foci neo-carcinogenesis by transplantation of cryopreserved ovarian tissue (Cadron *et al*., 2007).[19] Ultrasound-guided collection of oocytes. From ovary for *in vitro* maturation (IVM) and cryopreservation also has a risk of spreading the disease at the time of puncture of follicles. Considering the above-mentioned risks, these patients are left with almost no options to preserve their fertility. Harvesting oocytes from surgically removed ovaries and either cryopreserving them or creating embryos after IVM and Intracytoplasmic sperm injection (ICSI) for cryopreservation are the only options available to these patients. Cryopreservation of oocytes may be applicable to patients without male partners, whereas cryopreservation of embryos could be employed only in patients with male partners.

Collection of mature eggs at the time of oophorectomy has been attempted after COH followed by vitrification of these oocytes (Bocca *et al*., 2011; Fatemi *et al*., 2011).[20,21] However, collection of immature oocytes followed by IVM may be a safer approach. Huang *et al*., (2007)[22] collected immature oocytes from ovary after oophorectomy and subjected them to IVM. These authors vitrified resulting mature oocytes for future use by the patient. Embryos have been created after warming such vitrified oocytes followed by ICSI (Fadini *et al*., 2012)[23] and resulting embryos transferred to uterus, in a patient with ovarian adenocarcinoma. Nonetheless, they did not result in pregnancy. Embryos have been created from fresh oocytes harvested from ovary [Figure 1] followed by oophorectomy after IVM and ICSI in patients with endometrial carcinoma (Revel *et al*., 2004)[24] and advanced ovarian cancer (Prasath *et al*., 2008; Prasath *et al*., 2014)[25,26] as these patients had male partners at the time of oophorectomy. The embryos [Figure 2] were frozen as the patients had to undergo cancer therapy. Patients who underwent hysterectomy have to seek surrogacy (Revel *et al*., 2004; Prasath *et al*., 2008).[24,25] Patients, without hysterectomy, may use frozen embryos after completing treatment and cleared of cancer. Our team has published the first report on pregnancy and live birth from frozen-thawed embryos obtained from fresh oocytes, harvested

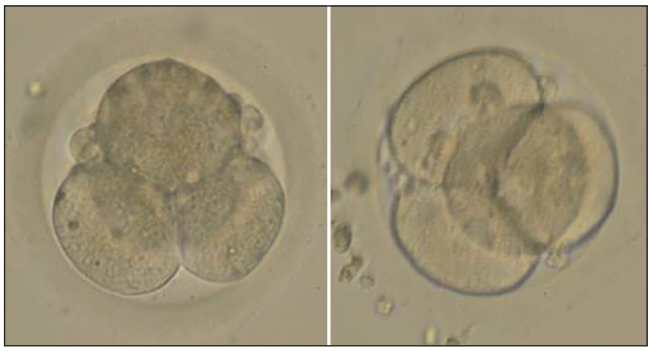

Figure 2: Four cell embryos from *in vitro* matured oocytes (Prasath *et al*., 2008)[25]

Table 1: Comparison of reports on *in vitro* maturation (IVM) of oocytes obtained from ovary after oophorectomy in uterine and ovarian cancer patients

	Revel *et al.*, (2004)[24]	Huang *et al.*, (2007)[22]	Prasath *et al.*, (2008)[25]	Fadini *et al.*, (2012)[23]	Prasath *et al.*, 2014[26]
Age	43	43	34	38	22
Type of cancer	Endometrial	Ovarian	Ovarian	Ovarian	Ovarian
Oocytes collected	17	4	6	3	4
In vitro matured	14	3	3	2 (frozen)	4
ICSI	14	Not done	3	2	4
Fertilized	6	Not done	2	1	4
Embryos frozen	5	3	2	0	3
Frozen embryo transfer (no. of embryos)	Not done	Not done	Not done	Done (1)	Done (2)
Pregnancy	—	—	—	No	Yes
Live birth	—	—	—	No	Yes (singleton)

from surgically removed ovary, after IVM and ICSI in a patient with advanced ovarian cancer (Prasath *et al*., 2014) [Table 1].[26]

CONCLUSION

Options to preserve fertility for patients with cancer of reproductive organs, such as ovary or uterus, are limited to harvesting oocytes from surgically removed ovary, followed by either cryopreserving oocytes if no male partner is available, or cryopreserving embryos after IVM and ICSI of oocytes if male partner is available. Surrogacy is the only option to use frozen embryos for patients with hysterectomy. Ovarian cancer patients who kept their uterus may bear pregnancy using frozen-thawed embryos.

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