

## Update on fertility preservation: new opportunities and challenges in the fight against infertility

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### Abstract

Infertility has been characterized as a disease by the World Health Organization (WHO) and reportedly affects about 10-12% of couples worldwide, while the incidence is even higher in Italy, at about 15%. The issue of iatrogenic infertility arising from treatments that can compromise an individual's reproductive capacity, it is necessary to inform patients of the possible damage on their future fertility and on the possibilities to preserve it. The complexities inherent in the various techniques and approaches aimed at preserving fertility should be expounded upon thoroughly to the patients, who should also receive proper psychological assistance and counseling, which ought to take into account the ethical distinctive challenges and the possible misgivings that may be caused in patients. Ovarian Tissue Cryopreservation (OTC) and ovarian tissue transplantation (OTT) can constitute a valuable part of the clinical armamentarium for preserving fertility, although the data are still inconclusive, particularly in over-36 patients. The multidisciplinary nature of the healthcare teams involved in such interventions is of paramount importance to optimize results.

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Dear Editor,

The World Health Organization (WHO) considers infertility a disease, and defines it as the absence of conception after 12/24 months of regular unprotected targeted sexual intercourse. Infertility in Italy affects about 15% of couples while, in the world, about 10-12%. In all cases of diseases and treatments that can compromise an individual's reproductive capacity, it is necessary to inform patients of the possible damage on their future fertility and on the possibilities to preserve it. For adult women, oocytes, embryos or ovarian tissue can be cryopreserved; for prepubescent girls and girls only cryopreservation of ovarian tissue. For adult men cryopreservation of seminal fluid while for prepubertal

boys only testicular tissue. Freezing techniques have allowed patients who need to preserve their fertility following a cancer diagnosis to have reasonably favorable prospects of preserving their ability to achieve motherhood (1, 2). Female patients, on which this writing is focused, usually require controlled ovarian stimulation with administration of Gonadotropin-releasing hormone (GnRH) antagonist (3) before the Human Chorionic Gonadotropin (HCG) trigger and consequent oocytes freezing using a vitrification technique (4, 5) in order to avoid the ovarian hyperstimulation syndrome (OHSS). Moreover, as for ovarian stimulation in women seeking fertility preservation for medical reasons, the GnRH antagonist protocol is recommended by virtue of its feasibility in urgent situations, short time and safety reasons. In this urgent time a random-start ovarian stimulation is helpful. In ovarian stimulation for fertility preservation in estrogen-sensitive diseases, the concomitant use of anti-estrogen therapy, such as letrozole, is probably recommended. Women should be informed of accurate, centre-specific expertise and live birth rates. They should also be informed that success rates after cryopreservation of oocytes at the time of a cancer diagnosis may be lower than in women without diagnosis of malignancies (6). A psychological counselling, pre-conception counselling and fertility treatment counselling should be considered for all patients (7). Women considering oocyte cryopreservation for age related fertility loss should be fully informed regarding the success rates, risks, benefits, costs and the possible long-term consequences, both in terms of physical and psychological health. In addition, embryo cryopreservation is an option for fertility preservation and women should be informed about the risk of losing reproductive autonomy, possible issues with stored embryos, centre-specific expertise and live birth rates. The considerably successful use of cryopreserved embryos has prompted researchers to further pursue such paths, although the debate on whether future children ought to be informed as to their biological origins is still open. In addition, other beginning-of-life ethics implications relative to the level of legal safeguards for gametes and embryos cannot be overlooked, and ought to be thoroughly elaborated on and discussed with patients, who need to be

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enabled to make decisions based on their own personal values and beliefs (8, 9). That being said, it is recommended to offer ovarian tissue cryopreservation (OTC) to patients undergoing moderate/high risk gonadotoxic treatment where oocyte/embryo cryopreservation is not feasible, or at patient preference. OTC should probably not be offered to patients with low ovarian reserve or advanced age considering the unfavourable benefit. (9). Efficiency performance of OTC procedure is questionable above 36 years of age. Patients who have already undergone low gonadotoxic treatment or a previous cycle of chemotherapy can be offered OTC as fertility preservation treatment and ovarian stimulation can be performed after OTC. As for ovarian transposition, it can be performed at the same time as OTC in patients who will receive pelvic irradiation. OTC is not recommended as primary FP procedure in transgender men but can be proposed as an experimental option when ovaries are removed during gender reassignment surgery.

In case of ovarian tissue transplantation (OTT) a one-step laparoscopy procedure has to be performed and it is generally considered safe, with no additional surgical risk. OTT at the orthotopic site is recommended to restore fertility. The decision to perform OTT in cancer patients requires a multidisciplinary approach (10). It is recommended to evaluate the presence of residual neoplastic cells in the ovarian cortex using appropriate techniques in all cancer survivors before OTT and patients should be informed about this risk. OTT is not recommended in cases where the ovary is involved in the malignancy. About pregnancy and OTT, no increased risk of congenital abnormalities has been reported following the procedure. OTT can be offered in BRCA patients as an alternative when egg or embryo freezing is not feasible, but the ovarian tissue must be completely removed after subsequent pregnancy. In women with breast cancer, GnRH agonists during chemotherapy should not be considered an option for fertility preservation instead of cryopreservation techniques. Preconception counselling and appropriate obstetric monitoring is recommended in women intending to become pregnant after gonadotoxic treatment.

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