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In this issue we present a recent publication that discusses ***established and experimental techniques of fertility preservation***. It also presents current data ***supporting the use of ovarian suppression by GnRH agonist*** for ovarian protection during chemotherapy. Data suggest that ***newer targeted therapies*** such as ***trastuzumab*** and ***imatinib*** do not increase the risk of infertility in patients with breast cancer. However, conception should be avoided during the course of targeted therapies Additionally, uptake of fertility services and barriers to fertility preservation in female patients of reproductive age are reviewed.

Advances in Fertility Preservation for Young Women with Cancer

Smith K L, Gracia C, Sokalska A, Moore H. 2018 ASCO Educational book

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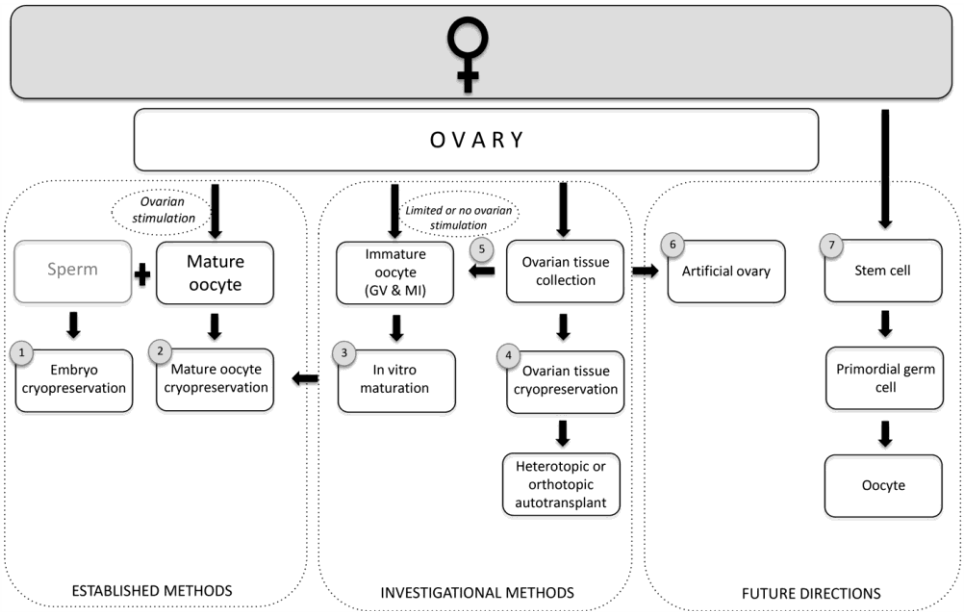
Introduction : Treatment- related infertility is an important cancer survivorship issue and is associated with depression and diminished quality of life. The available data indicate that female cancer survivors achieve pregnancy at lower rates than un-affected women in the general population, due to chemotherapy (CT) and age related effects on ovarian reserve underpinning the importance of fertility preservation (FP). Recent advances in reproductive health care provide the opportunity to preserve fertility prior to initiation of cancer therapy. Long term follow up of up to 7 years suggest that pregnancy after cancer treatment does not increase the risk of cancer recurrence, even in women with a history of hormone receptor positive cancer. Patient's express a desire for more information about fertility issues and feel their fertility concerns are not adequately addressed by their oncology care teams.

Figure 1 Overview of currently available established & investigational ART for fertility preservation



Techniques: *Oocyte and embryo cryopreservation* in post-pubertal females are established FP techniques requiring ovarian stimulation (OS). Goal is to obtain a high no. of oocytes in one cycle while minimizing risk of ovarian hyperstimulation syndrome, which can delay and complicate ca therapy.

Ovarian tissue cryopreservation – requires a surgical procedure. It is suitable for patients requiring immediate cancer therapy and pre-pubertal girls. Currently considered experimental in some countries though over 130 live births have been reported after

ovarian tissue transplantation. Risk of cancer reseeding exists. Not recommended for women with blood- borne malignancies, ovarian cancers, malignancies that can result in metastasis to the ovary, or an inherent predisposition to ovarian cancer.

In VItro Maturation of immature oocytes- reported mainly in PCOS patients, can be an option for patients requiring urgent CT and those with hormone sensitive Ca. May be done with or without OS.

Future Strategies to prevent reseeding of ca cells – a)Isolation of immature oocytes from ovarian tissue followed by in vitro maturation and IVF . One live birth reported. *b)* isolation of ovarian follicles followed by in vitro development of primordial follicles, or creating an artificial ovary and grafting it to the pelvis. c) development of primordial germ cells from transformed in vitro *stem cells*. Live birth reported in animals but no human data available.

Protocol of Choice of COS: Using a gonadotropin-releasing hormone (GnRH) *antagonist protocol with a GnRH agonist to trigger* final maturation of oocytes may reduce the risk of ovarian hyperstimulation syndrome. Random-start protocol"(Initiation of OS at any time of the menstrual cycle) prevents delay in ca therapy without compromising procedure. **For hormone sensitive cancers**- aromatase inhibitor Letrozole is added during OS to lower circulating E2 levels. Tamoxifen has also been used in COS of BC patients.

Reproductive Outcome: ***Embryos*** - 45% LBR per FET has been reported. ***Oocytes***: LBR per oocyte thawed is 6.5%, the cumulative LBR increases with no. of oocytes CP, reaching a plateau at 25. Limited data on oocytes CP for FP suggest that success rates are comparable to the general population. ART results with autologous oocytes after CT are low compared to non-cancer patients. ***Preimplantation genetic testing*** may allow couples to avoid passing a known *BRCA* mutation to their offspring.

Ovarian protection: GnRH agonists are thought to attenuate follicular atresia by preventing increased follicular recruitment and accelerated atresia induced by CT and possibly by decreasing blood flow. Use of GnRH agonists for ovarian suppression has been the subject of controversy. Restoration of menstrual function is achieved though restoration of fertility is doubtful. The Prevention of Early Menopause Study (POEMS)(2015) a large randomized study which included only HR negative BC patients reported a 70% reduction in risk of ovarian failure. 8% in goserelin arm reported ovarian failure compared with 22% in controls. Goserelin use was also associated with a significantly higher likelihood of achieving pregnancy after BC treatment (odds ratio 2.23; p = .03). Amenorrhea and postmenopausal hormone levels at 2 years follow-up were used to define ovarian failure. The OPTION trial (2017) also reported ***a significantly lower rate of premature ovarian insufficiency with use of goserelin during CT (18.5% vs. 34.8%; p = .048).*** AMH levels however were markedly reduced in both study arms raising concerns about the ability of agonist to protect fertility. A recent meta-analysis by Lambertini et al 2017 demonstrated a 62% reduction in the odds of ovarian failure with use of agonist. ***No detriment to disease-free or overall survival outcomes was observed regardless of hormone-receptor status***. RCT's of BC that have reported on subsequent pregnancies, show an approximate 83% increase in the likelihood of achieving pregnancy with ovarian protection compared with control groups. Use of GnRH agonist in patients with lymphoma has not shown a benefit. Use of GnRH agonist for ovarian protection has been endorsed as an option for fertility preservation by guidelines issued by some organizations, although not fully by ASCO.

Utilization of Fertility Services: Despite rapidly growing evidence regarding fertility preservation options and treatment guidelines supporting fertility preservation, few patients currently pursue fertility preservation. Oncologists and fertility specialists must together develop strategies to increase access to and use of fertility preservation by interested patients.

Key Message:

1. Guidelines endorse the use of ART to preserve fertility in young female cancer patients.
2. Guidelines recommend that oncology providers counsel patients about the risk of treatment-related infertility and FP interventions, and refer patients interested in FP to fertility specialists.
3. Both ART & ovarian suppression should be suggested, selection of FP intervention should be individualized.
4. Potential strategies to increase utility of FP include developing educational materials, having dedicated counsellors, developing institutional fertility programs and standardized institutional processes to identify patients for FP and mandating that oncology providers document discussing fertility issues in the medical record.