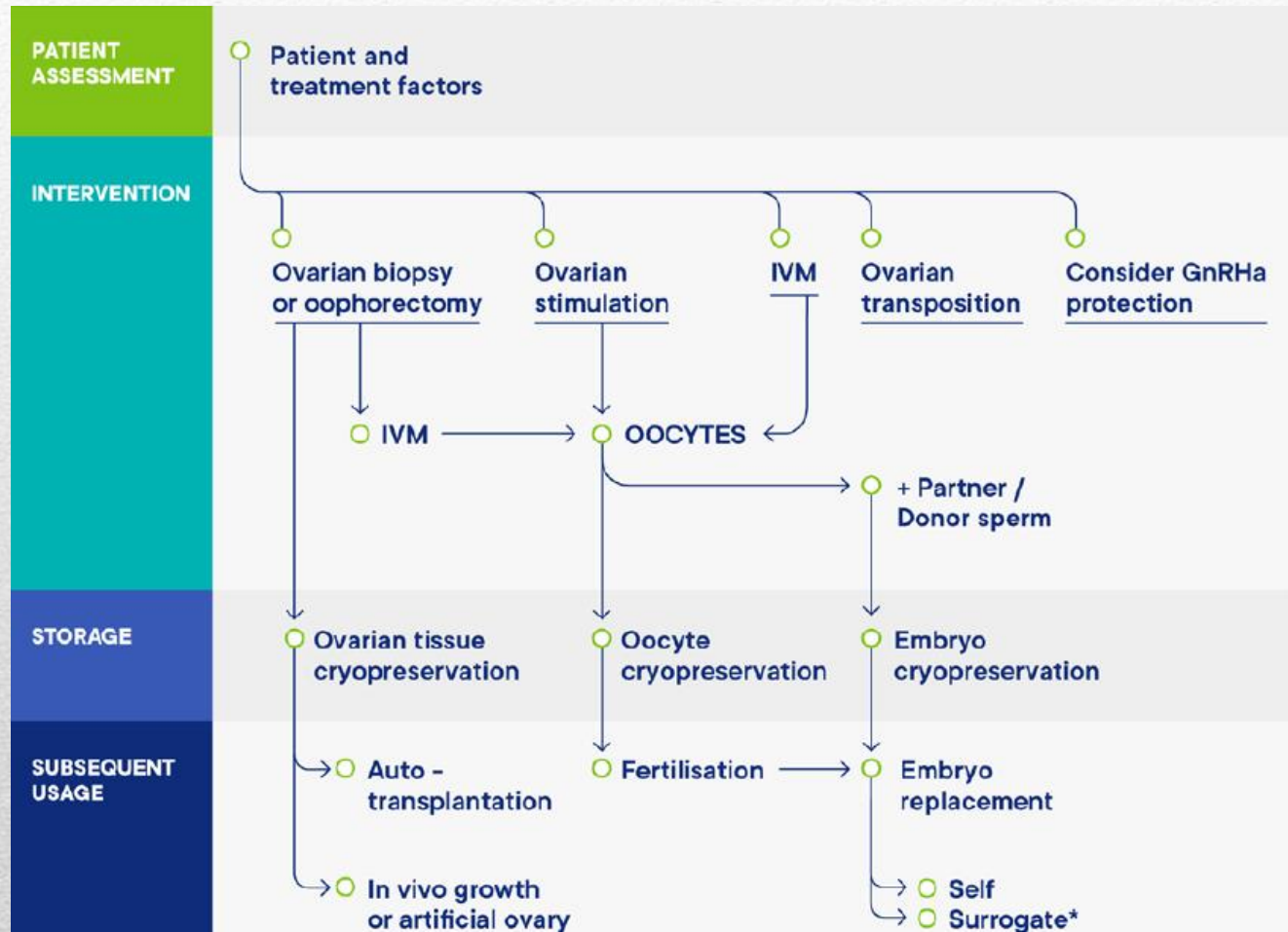


Fertility preservati

Dr: HASHEMI

Fellowship of infertility

Options for FP



- Ovarian stimulation for FP is usually an **urgent** procedure and evidence on feasibility, efficacy and safety of the methods is needed.
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Novel approaches have been suggested for specific cases or patient groups, such as random-start ovarian stimulation, and ovarian stimulation in the context of estrogen-sensitive cancer

- For **ovarian stimulation** in women seeking FP for medical reasons the **GnRH antagonist** protocol is recommended for its feasibility in urgent situations, short time and safety reasons .

Ovarian stimulation cycles initiated in the **luteal** were **slightly longer and required higher gonadotropin doses** when compared with stimulation started in the follicular phase .

- Peak serum estradiol and number of oocytes recovered did not differ between phases of the cycle at which OS was started.
 - Oocytes obtained in cycles initiated in the luteal phase fertilized more efficiently.
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- No conclusion can be drawn on pregnancy and live birth rates regarding the very small number of patients and the extremely low utilization rates of cryopreserved oocytes and embryos in cancer patients.
-

Double stimulation

- It involves 2 stimulation protocols within the same menstrual cycle: the first starting in the follicular phase, then second immediately after the oocyte pick up, in the luteal phase of the same cycle.
 - poor responder patients or cases for urgent fertility preservation.
-

- **Quality of oocytes retrieved** in the second stimulation appears to be as good as those retrieved in the first stimulation (same euploid embryo rate).=
 - The **cumulative LBR was higher** (15% vs 7%) as was the proportion of **euploid blastocysts** (31% vs 14%) in the group that underwent dual stimulation
-

Ovarian stimulation with potentially safer protocols aiming at reducing estrogenic effects and risks

- There are no data demonstrating an adverse effect of ovarian stimulation for FP in women with breast cancer.
-

- ovarian stimulation with letrozole
 - Peak estradiol concentrations: low
 - Oocyte yield between aromatase inhibitor protocols and conventional stimulation := or low
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- Compared ovarian stimulation with letrozole to that with tamoxifen:
 - The numbers of mature oocytes retrieved were lower when stimulation was performed with tamoxifen than with letrozole
-

- For ovarian stimulation in transgender men aiming at oocyte cryopreservation, GnRH antagonist protocols can be considered as they have been shown to be feasible and with numbers of oocytes retrieved comparable to those obtained in cisgender women when individuals have stopped previous treatment with testosterone
-

Efficacy of cryopreserved oocytes for fertility preservation

- Both age and indication for oocyte cryopreservation were found to have a marked impact on the cumulative live birth rate.
-

- The oocyte cryopreservation cycles were indicated by cancer in 18% of cases whereas 66% were for age-related fertility loss.
 - Fertilization rates after warming were about 67%, and 337 live births from 857 warming cycles were reported for all indications combined, with a pregnancy rate of 39.3%
-

- Effect of oncologic disease vs non-oncologic disease in reproductive outcome of oocyte vitrification cycles:
 - Similar return rate of 27% regardless of benign or malignant indication .
 - Significantly lower CLBR was found after warming cycles in women with oncologic versus benign indications .
-

Effect of type of malignancy

- Recent studies have not found any conclusive data to indicate an effect of the type of cancer in the outcome of ovarian stimulation aimed at FP
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Safety and risks

- Period of about 2-weeks has been needed in general to obtain oocytes .
 - An acceptable time span between diagnosis and initiation of cancer therapy in most cases .
-

- **General risks of ovarian stimulation and oocyte pick-up :**
 - Altered endocrine environment, and risks for thrombosis, hemorrhage and infection should be considered in all cases.
-

- The risks of **thrombotic complications** may be increased in women with certain diseases including malignant conditions in general, and autoimmune or rare diseases, as reported in women with GATA2 deficiency
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- Patients suffering from diseases featuring low platelet counts or lymphopenia may present with inherent higher risks of **bleeding and/or infection following transvaginal puncture procedures for oocyte pick-up.**
-

- OHSS should be avoided in women undergoing FP for medical reasons due to theoretically increased risks of complications such as thrombosis.
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Use of aromatase inhibitors for FP

- Safer for women with endometrial hyperplasia or borderline ovarian tumours
 - Transgender men, to reduce estrogenic effects and the worsening of gender dysphoria
 - Patients with increased inherent thrombosis risk
 - Minimize the risk of OHSS with letrozole is the use of GnRH agonist for oocyte trigger instead of hCG
-

Potential risks to offspring associated with oocyte cryopreservation

- Do not have an increased risk of **congenital anomalies**
 - Long-term cryopreservation does not increase **embryonic aneuploidy** when compared to fresh oocytes
 - While children conceived from assisted reproduction have an elevated risk of adverse birth outcomes. increased risks are related to the subfertility of the couple.
-

Oocyte cryopreservation for age-related fertility loss

- Gives people more time to prepare, become financially secure, and women will not rush into reproducing when they are not ready or they have not met the ‘right’ partner.
 - Reduce the incidence of aneuploidy associated with older motherhood.
-

Issues with oocyte cryopreservation for age-related fertility loss

Success rates

- Before they were 35 years old : 42.8% CLBR from 10 oocytes
 - Over 35 :
 - CLBR of 25,2% with 10 oocytes frozen
-



Obstetric risks:

- prematurity, low birth weight and small for gestational age in children born after transfer of cryopreserved embryos, compared to children born after fresh embryo transfers .
 - increased risks of being large for gestational age, having a birth weight >4000 g and also a higher risk of hypertensive disorders during pregnancy were present in the cryopreservation group
-

Ovarian tissue cryopreservation

- feasible within a short time frame in both post- and pre-pubertal patients and does not require any preceding drug treatment.
-

- **The advantages of OTC:**
 - possibility to restore **natural ovarian function** (including non-reproductive endocrine effects) after ovarian tissue transplantation (OTT)
 - achieve (several) **natural pregnancies** without further medical intervention
-

- One of the major advantages of OTC compared to oocyte/embryo cryopreservation is the possibility to perform the procedure after starting chemotherapy treatment.
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Patient selection criteria

- Edinburgh criteria: patients younger than 35 years old with >50% of risk of chemotherapy-induced ovarian failure, no previous gonadotoxic treatment, no surgical contraindication and a realistic chance of survival.
-

- None of the patients over 36 years old at the time of OTC achieved pregnancy while 30% of the patients who achieved pregnancy after using vitrified oocytes were older than 36 years old at the time of FP procedure.
 - Similar success rates in terms of fertility restoration for OTC and oocyte vitrification in younger patients.
-

- **Indications :**

- More than 80% of the patients referred for OTC are patients scheduled to receive gonadotropic therapy.
 - benign conditions that potentially affect the ovarian reserve either due to the disease itself, such as genetic disorders (Turner syndrome, galactosaemia), or due to gonadotoxic treatments, such as alkylating agents for autoimmune disorders (systemic lupus erythematosus [SLE]) or as a conditioning regimen before hematopoietic stem cell transplantation (HSCT) (in sickle cell anaemia, thalassaemia)
-

The ovarian tissue cryopreservation (OTC) procedure

- Either an ovarian cortex biopsy (the location of the primordial follicle pool) or one whole ovary can be retrieved at any time during the menstrual cycle and the cortex cryopreserved for future restoration of ovarian function.
-

- surgery can be performed in the referring hospital and the ovarian tissue transported (1 to 20h) under strict conditions to a qualified fertility clinic laboratory/tissue bank for processing and cryopreservation
-

- Laparoscopy is the most commonly used approach to collect the tissue, although mini-laparotomy was also described in children.
 - For ovarian biopsy, large fragments of cortex at a distance from the hilum and from any large visible follicles or corpus luteum should be harvested and careful hemostasis should be achieved after tissue removal
-

The ovarian tissue transplantation (OTT) procedure

- Orthotopic transplantation into the remaining ovary, broad ligament, or ovarian peritoneal pocket is the most common procedure.
 - After auto-transplantation of ovarian tissue at an orthotopic site, more than 60% of pregnancies occurred after natural conception in patients treated for cancer or benign conditions
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- Pregnancies obtained after transplantation at the peritoneal site usually required IVF treatment.
 - Specific ovarian risks (such as BRCA mutation carriers), the decision regarding the site of transplantation should also take into consideration the need to remove the grafted ovary after pregnancy
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- Transplantation at the heterotopic site, such as subcutaneously in the forearm or to the abdominal wall, is less invasive and efficient to restore endocrine function .
 - However, only one live birth has been reported so far after transplantation to the anterior abdominal wall
-

- Success rate: younger at OTC
 - amount of transplanted tissue and the follicular density
 - One group has described criteria based on the ovarian reserve under which OTC should not be performed, considering the unfavourable risk/benefit balance. These criteria are based on the 5th centile of AMH and AFC in cancer patients younger than 35 years (0.4 ng/ml and 5 visible follicles, respectively)
-

- There is no generally accepted upper age limit for the OTT procedure, and it has been performed in women up to 47 years old.
 - 1/3 of the ovary was usually used for grafting but also reported that 45 patients required two OTT procedures to achieve pregnancy
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- OTC was performed on the same day as oocyte pick-up in 14 patients.
 - OTC can be also be associated with ovarian transposition in patients who will be treated with pelvic irradiation
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- 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.
-

Genetic disorders

- OTC has been offered also in young patients (often children) with genetic disorders when there is an associated risk of POI such as in galactosemia, Turner syndrome and Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) syndrome
-

- Published cases of the transplantation of frozen-thawed ovarian tissue were recently summarized.
 - Eighty seven live births were reported, but data on health of the baby were only available for 40 births .
 - All these children were born healthy, except one who was affected by foetal arthrogryposis.
-

Replacing ovarian tissue: safety concerns

- Surgical complications
 - Risk of reintroducing malignancy
 - Oncological outcomes in hormonal-sensitive diseases
 - Risk for offspring.
 - Long-term risk of OTT
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- There appears to be no increased risk of congenital abnormalities for children born after OTT.
-

- OTT is probably not recommended in patients treated for borderline ovarian tumour (BOT) or ovarian cancer
-

Recommendations

- The decision to perform OTT in oncological patients requires a multidisciplinary approach.
 - It is recommended to evaluate the presence of residual neoplastic cells in the ovarian cortex (and in the residual medulla when available) 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
-

Recommendation

- OTT and pregnancy can be considered in hormone-sensitive tumours such as endometrial cancer treated by fertility-sparing strategy or breast cancer, after complete remission of the disease
-

Recommendation

- Long-term risks in human are considered to be low but a long-term follow-up of patients after OTT is recommended .
 - 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
-

Disease	Considerations for OTC/OTT	Recommendation for OTT
Ovarian or adnexal tumour	<p>OTC should only be carried out after careful consideration, when other options are not feasible, bearing in mind that replacement may not be available to the patient in the foreseeable future due to the high risk of recurrence and the risk of cryopreserved ovarian tissue involvement.</p>	<p>OTT is <u>probably not recommended</u> considering the high risk of ovarian tissue involvement. The safety of OTT with removal after pregnancy needs to be further investigated.</p>
Leukaemia	<p>Ovarian tissue should ideally be collected at the time of complete bone marrow remission (after first chemotherapy regimen) and it should be tested using molecular detection techniques before OTT. If molecular markers are not available, xenograft experiments should be performed.</p>	<p>OTT should be considered with <u>extreme caution</u> considering the high risk of ovarian involvement by leukaemia cells. Additional data are needed regarding the safety of OTT.</p>
Tumours of the central nervous system (CNS)	<p>Data are limited regarding the risk of reintroducing the disease in patients treated for CNS tumours. Medulloblastoma and neuroblastoma are considered at higher risk.</p>	<p>OTT should be considered with <u>extreme caution</u>. Additional data are needed regarding the safety of OTT.</p>
Non-Hodgkin Lymphoma	<p>OTC/OTT can be performed in patients with non-Hodgkin lymphoma with no evidence of distant metastasis or pelvic involvement at diagnosis.</p>	<p>OTT appears to be <u>safe</u> if pelvic involvement is excluded at diagnosis. OTT can be considered after appropriate ovarian tissue testing using histology and molecular approaches when available.</p>
Hodgkin Lymphoma	<p>OTC/OTT appears to be safe in patients with Hodgkin lymphoma when pelvic involvement was excluded at diagnosis.</p>	<p>OTT appears to be <u>safe</u> if ovarian involvement is excluded at diagnosis. OTT can be considered after appropriate ovarian tissue testing using histology.</p>
Cervical tumours	<p>Ovarian involvement is rare at diagnosis, and more frequent in adenocarcinoma than in squamous cell carcinoma.</p>	<p>OTT appears to be <u>safe</u> in patients treated with fertility-sparing strategy although more data are requested regarding the risk of ovarian tissue involvement in patients after OTC.</p>

In vitro maturation (IVM)

- Mainly used for women with polycystic ovary syndrome (PCOS) to avoid the risk of ovarian hyperstimulation syndrome (OHSS).
 - IVM involves culture (for 24 to 48h) of immature cumulus-oocyte complexes (COCs) recovered from small antral follicles of patients that received no or mild FSH stimulation.
-

- In a fertility preservation programme, IVM can be offered as an **alternative** when conventional ovarian stimulation is contraindicated, or when the time available before the start of gonadotoxic treatment is short and cannot be delayed for ovarian stimulation treatment .
-

IVM

- Exogenous FSH administration may be avoided or minimally administered, and that oocytes can be retrieved independently of the phase of the menstrual cycle.
-

Live births following IVM

- About 10 live births have been reported from embryos derived from vitrified IVM oocytes from infertile patients.
-

Although the overall success rates with in vitro matured oocytes are lower compared to IVF, the births of over 5000 children have been reported with no increase in congenital anomalies when compared to IVF children

GnRH agonists

- **Breast cancer** :In women who received chemotherapy with or without GnRH agonist, chemotherapy-induced POI rates were 14.1% and 30.9%, respectively .
 - The ovarian protective effect of GnRH agonists was observed irrespective of patients' age at the time of treatment, estrogen receptor status, type and duration of chemotherapy.
-

- The 5-year cumulative incidence of pregnancy was significantly higher in the chemotherapy plus GnRH agonist arm as compared to the chemotherapy alone arm .
 - antral follicle count recovered faster and to a greater degree for those who received GnRH agonists during .
-

Newly diagnosed breast cancer in premenopausal women

Counseling about gonadotoxicity risk

Desire to preserve fertility

No desire to preserve fertility

Desire to preserve ovarian function

Availability >2 weeks

Availability <2 weeks

Yes

Preferably at ≤40 years

Preferably at ≤36 years

Preferably at ≤45 years

Stimulation followed by oocyte cryopreservation

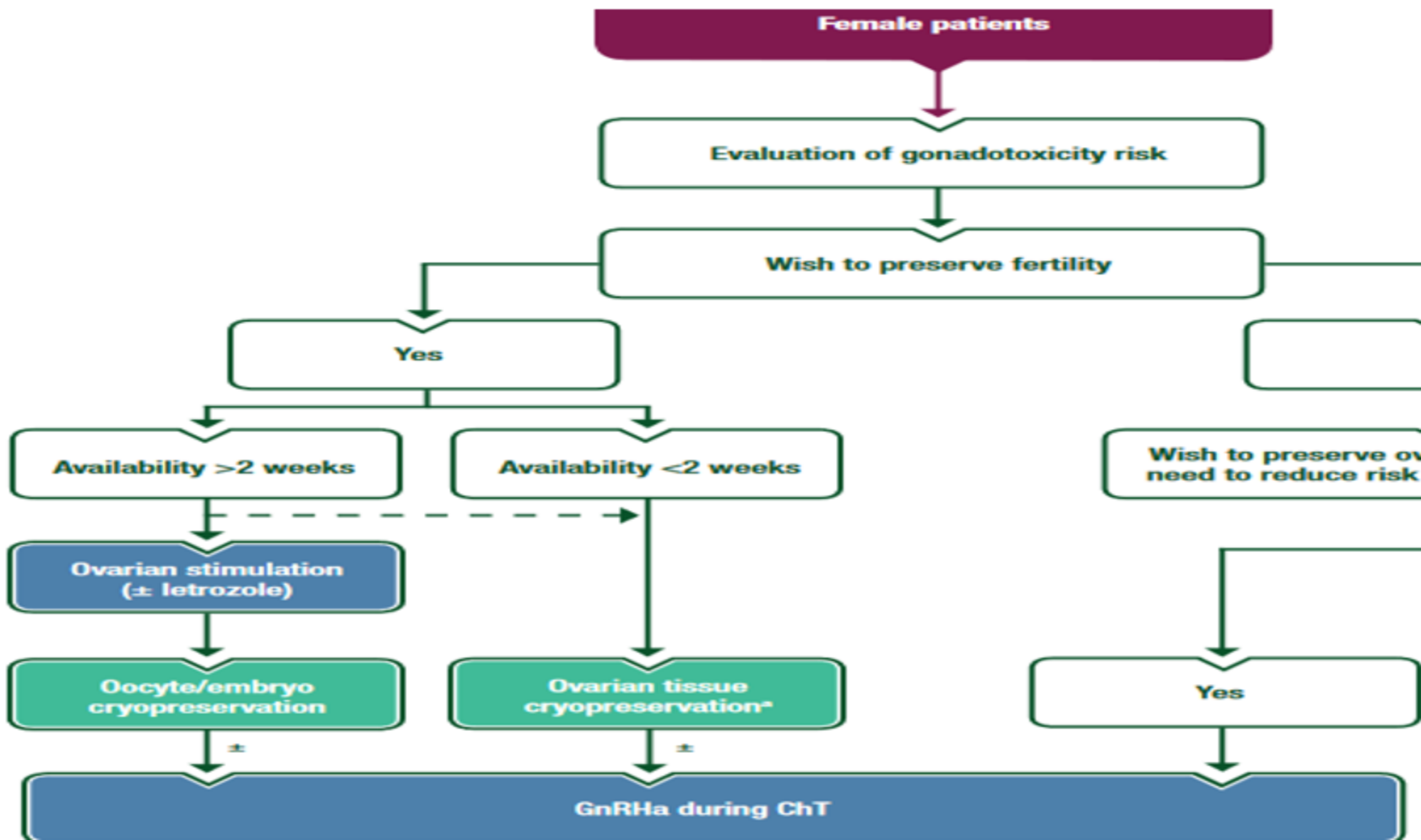
Ovarian tissue cryopreservation

GnRHa during chemotherapy

+/-

+/-

Counseling about adequate contraception during active treatment and follow-up



- **Regarding safety**, the administration of GnRH agonists is associated with significant higher rates of hot flushes and sweating .
 - Bone turnover is increased during administration of GnRH agonists with normalization after cessation of treatment and with the potential to protect against longstanding altered bone turnover associated with POI
-

- In premenopausal breast cancer patients and particularly in those with estrogen receptor-positive disease, there are potential **safety concerns** regarding possible antagonism between GnRH agonists and chemotherapy.
 - However, no difference in disease-free survival and a non-significant trend towards better overall survival with concurrent use of GnRH agonists during chemotherapy
-

Recommendation

Lymphoma

- No significant difference in POI rates was observed between lymphoma patients who received chemotherapy with or without concurrent GnRH agonists .
 - Significantly higher AMH levels were observed in patients who received GnRH agonists during chemotherapy at one year follow-up, but not at later follow-up (2-4 and 5-7 years)
-

- An additional medical benefit of administering GnRH agonists during chemotherapy is **prevention of heavy menstrual bleeding** which may be of value for patients receiving chemotherapy regimens with high bone marrow toxicity.
-

Ovarian cancer

- Six months after chemotherapy, all the patients who received GnRH agonists during chemotherapy had normal menstrual bleeding, while 33% of those treated with systemic cytotoxic therapy alone had treatment-induced POI.
 - No information on post-treatment pregnancies was available.
-

Recommendation

- In malignancies other than breast cancer, GnRH agonists should not be routinely offered as an option for ovarian function protection and fertility preservation without discussion of the uncertainty about its benefit.
-

- In women with breast cancer, GnRH agonists during chemotherapy should not be considered an option for fertility preservation instead of cryopreservation techniques .
-

Recommendation

- GnRH agonists during chemotherapy may be considered as an option for ovarian function protection in premenopausal patients with autoimmune diseases receiving cyclophosphamide.
 - However, it should be acknowledged that limited data are available in this setting.
-

Ovarian transposition

- **Preservation of ovarian function:** Successful preservation of ovarian function after ovarian transposition and external-beam radiotherapy (with or without brachytherapy) ranged from 20 to 100% (26 studies n = 401), after a median follow-up time ranging from 7 to 102 months.
 - A higher frequency of preserved ovarian function was found in women who received brachytherapy only, from 63.6 to 100% (8 studies, n=148).
 - In patients who received radiation therapy and chemotherapy, preservation of ovarian function ranged from 0 to 69.2%
-

- **Pregnancy after ovarian transposition**
 - Several pregnancies have been reported after ovarian transposition, including natural conceptions
-

Obstetric outcomes

- women previously treated for cancer higher rates of postpartum haemorrhage, operative or assisted delivery, and preterm birth .
-

- The risks of early death or stillbirth were not increased after adjustment for prematurity, and there was no increased risk of congenital or chromosomal abnormality .
 - An increased risk of stillbirth within three years after the cancer diagnosis .
-

- The risk of stillbirth and neonatal death was significantly decreased among second children as compared to the first born, suggesting that any adverse effect associated with cancer treatments may diminish with time.
-

Effect of chemotherapy

- Chemotherapy is not associated with adverse pregnancy outcomes .
-

Effects of chemotherapy for childhood cancer on subsequent pregnancy outcomes

- women who conceived ≥ 1 year after starting chemotherapy without radiation or ≥ 2 years after chemotherapy with radiation did not have an increased risk of preterm birth .
-

Recommendation

- An interval of at least 1 year following chemotherapy completion is suggested before attempting a pregnancy in order to reduce the risk of pregnancy complications
-

Effect of Pelvic radiotherapy

- Females treated with pelvic radiation for childhood cancers have an increased rate of uterine dysfunction leading to pregnancy loss, preterm birth and low birth weight.
 - These pregnancy-related complications are related with reduced uterine volume, damage of uterine vessels, myometrial fibrosis, endometrial injury.
-

- High-dose pelvic irradiation can permanently impair growth and blood flow to the uterus resulting in a reduced uterine volume; these effects of radiation are dependent on age.
 - Uterine or ovarian irradiation with doses ≥ 2.5 Gy greatly increased the risk of stillbirth or neonatal death (12-fold) in women treated before menarche.
-

- Effect of adulthood radiation effect on pregnancy, the incidence of **spontaneous abortion** (37% versus 7%) and **preterm birth** (63% versus 18%) were significantly higher **in total body irradiation (TBI)** recipients when compared to the chemotherapy-only group.
-

- Radiotherapy-induced structural and functional changes to the uterus ($> 5\text{Gy}$) may adversely affect implantation and maintenance of pregnancy increasing the risk of placental attachment disorders (placenta accreta or placenta percreta), low birth weight.
-

Recommendations

- After completion of the recommended treatment, pregnancy is safe in women who have survived breast cancer.
 - This is independent of estrogen receptor status of the tumour.
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- Reliable non-hormonal contraception is mandatory during tamoxifen treatment.
 - It is recommended to stop tamoxifen for at least 3 months before attempting pregnancy .
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THANKS
