IN THE NAME OF GOD

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Female Fertility Preservation

Guideline of the European Society of Human Reproduction and Embryology

Fertility Preservation Indications

- Post pubertal women diagnosed with cancer undergoing gonadotoxic treatments
- Post pubertal women with benign diseases undergoing gonadotoxic treatments (including surgery) or with conditions from which they will lose their fertility prematurely, e.g. Turner syndrome(mosaism form)

- Women requesting oocyte cryopreservation for age-related fertility loss

Clinicians may consider referring Fertility Preversation patients who present risk factors for psychological distress for psychological support and counselling .

Gonadotoxic treatments

- Treatments for cancer and other medical conditions may cause gonadal damage by directly affecting the growing and non-growing ovarian follicle pool, the ovarian stroma or the blood supply to the ovary
- premature ovarian insufficiency
- Infertility

- Most of the studies that assessed ovarian reserve markers to estimate treatment-induced gonadotoxicity have focused on AMH during and after treatment completion

- The AMH level dramatically falls within 2 weeks after gonadotoxic treatment, even after low gonadotoxic treatment initiation (ABVD), and recovery takes usually at least 6 months

- It is the type and dose of chemotherapy that are the major factors determining risk of treatment-induced POI
- In terms of patient characteristics, age is the most important factor affecting the risk of gonadotoxicity
- Pre-treatment ovarian reserve, linked with age
- Hereditary factors, with most of the evidence on the impact of germline mutations in the BRCA genes .

- Two studies have shown that pre-treatment AMH levels lower than 1.9ng/ml lead to long-term (longer than 5 years) loss of ovarian function

- A narrative review concluded that taking into consideration age and body mass index (BMI) together with AMH levels can increase the accuracy of the prediction of cancer-related ovarian failure

- The gonadotoxicity of radiotherapy is dependent on the field of radiation, its dose and fractionation.

Radiotherapy can directly damage ovarian follicles and other ovarian tissues, but may also cause adverse effects on other reproductive organs, notably the uterus

- Apart from gonadotoxic treatments, the disease itself (e.g. lymphoma or endometriosis) can be associated with gonadal damage and diminished ovarian reserve

Breast cancer

- The highest risk of gonadotoxicity with the use of gonadotoxic systemic therapies in early breast cancer patients is associated with the administration of the alkylating agent cyclophosphamide, commonly given as part of (neo)adjuvant chemotherapy regimens

- cyclophosphamide-based regimens are associated :
- significantly higher risk of POI
- more than double the chances of developing treatment-induced amenorrhoea

- The use of anthracycline-based or taxane-based regimens significantly increased the risk of treatment-induced amenorrhoea .

- With the administration of all these chemotherapy agents, AMH levels fall to undetectable levels in most women and generally persist at very low levels after treatment completion, with the extent of recovery determined by age and pre-treatment AMH levels .

Targeted treatments

- Limited evidence
- The two studies reporting rates of treatment-induced amenorrhoea in patients receiving chemotherapy with anthracycline- and/or taxane-based regimens plus the anti-HER2 agents(trastuzumab) and/or lapatinib have suggested likely gonadal safety of these agents

Tamoxifen

Several studies have shown no difference in AMH levels between patients receiving tamoxifen following chemotherapy or not .

Endocrine treatments

- GnRH analogue treatment can suppress AMH levels.

- Importantly, the ovarian function may recover after use of an aromatase inhibitor alone in premenopausal women (even those beyond 45 years of age)

Haematological cancers

- The cumulative POI risk with the use of alkylating-based chemotherapy was 60% while it was only 3% for women exposed to non-alkylating regimens .

- A linear dose-response relationship between alkylating chemotherapy and occurrence of POI was observed

- At one year after ABVD completion, AMH levels had returned to pre-treatment concentrations with no changes at longer follow-up.

- However, age strongly affected the extent of AMH recovery after ABVD:
- Full recovery was observed in women younger than 35 years, with only partial recovery in patients ≥35 years.
- In patients treated with BEACOPP, there was very little recovery in AMH levels overall, with further increased risk of POI in patients older than 35 years.

It is unknown that whether extent the disease itself may contribute to increasing the risk of treatment-induced gonadotoxicity .

Gynecological cancers

Overall, chemotherapy regimens used for treating young women with gynecological cancers can be considered associated with a low risk of gonadotoxicity

RISK CATEGORY	TYPE OF GONADOTOXIC TREATMENT
High risk (> 80% risk of treatment-induced amenorrhoea)	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged ≥ 40 years • Conditioning regimens for HSC transplantation with cyclophosphamide and/or TBI in patients with haematological cancers • Abdominal and pelvic radiotherapy to a field that includes the ovaries
Intermediate risk (40%-60% risk of treatment- induced amenorrhoea)	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged 30-39 years • Alkylating agent-based regimens (e.g. MOPP, RSQB, BEACOPP, CHOP, CHOPE) in lymphoma patients
Low risk (< 20% risk of treatment-induced amenorrhoea)	• Cyclophosphamide-based regimens (with anthracyclines and/or taxanes: (F)EC/(F)AC alone or followed by T or P, TC) in breast cancer patients aged ≤ 30 years • Non-alkylating agent-based regimens (e.g. ABVD or EBVP) in lymphoma patients aged ≥ 32 years • BEP / EP in patients with non-epithelial ovarian cancers • FOLFOX, XELOX or capecitabine in patients with colorectal cancers • Multi-agent chemotherapy (EMA-CO and platinum-based combinations) for gestational trophoblastic tumours • Radioactive iodine (I-131) in patients with thyroid cancer
Very low or no risk	• Targeted agents (trastuzumab, lapatinib and rituximab) ? • Tamoxifen and GnRH analogue • Non-alkylating agent-based regimens (e.g. ABVD or EBVP) in lymphoma patients aged < 32 years • Single-agent methotrexate
Unknown risk	• Platinum- and taxane-based chemotherapy in patients with gynaecological and lung cancers • Majority of targeted therapies (monoclonal antibodies and small molecules like tyrosine kinase inhibitors) and immunotherapeutic agents

FACTORS THAT INCREASE THE RISK.

- → Older age at diagnosis[1]
- → Lower pre-treatment AMH levels[2]
- → Type and dose of treatment (chemotherapy and radiotherapy)[3]

ANTICANCER TREATMENT → **RISK OF GONADOTOXICITY**

FACTORS FOR WHICH THERE IS INSUFFICIENT EVIDENCE TO MAKE A CONCLUSION:

- → Smoking history[4]
- → Body mass index[4]
- → Carrying germline *BRCA* mutations[5]
- → Cancer diagnosis[6]
- → Targeted agents[7]

Supporting studies/reviews

1. Breast cancer,(Silva et al., 2016); Hodgkin Lymphoma, (van der Kaaij et al., 2012)
2. Breast cancer, (Anderson and Cameron, 2011, Silva et al., 2016, Anderson et al., 2017b, Dezellus et al., 2017, Freour et al., 2017) (AMH) (evidence in BC)
3. Breast cancer, (Lambertini et al., 2017a); Hodgkin Lymphoma, (van der Kaaij et al., 2012); Haematological cancers, (Tauchmanova et al., 2003, Akhtar et al., 2015)
4. Breast cancer, (Abusief et al., 2012)
5. Breast cancer (Valentini et al., 2013, Lambertini et al., 2019c)
6. Lymphoma, (Lawrenz et al., 2012, Lekovich et al., 2016)
7. Breast cancer (endocrine therapies), (Bernhard et al., 2007, Anderson et al., 2017b, Dezellus et al., 2017, Freour et al., 2017, Lambertini et al., 2019c); Breast cancer (anti-HER2), (Ruddy et al., 2015, Lambertini et al., *2019a)*

Systemic Lupus Erythematosus (SLE)

. Patients with SLE already present poor ovarian reserve and function regardless of the activity of the disease or exposure to SLE therapy

- Menstrual irregularities, mostly related to anovulation, are however associated with disease activity

Patients with benign diseases

- Fertility preservation may be challenging in these patients due to severe health conditions
- long-term therapy (i.e. hydroxyurea)
- high risk of thrombosis and/or the genetic context

Benign haematological diseases

- Haematopoietic stem cell transplantation (HSCT) remains the only curative option for several benign haematological diseases such as thalassemia
- sickle cell disease, aplastic anaemia,
- Fanconi anaemia or myeloproliferative syndromes

- A regimen for HSCT includes high dose alkylating agents and is associated with high risk of permanent amenorrhoea

Recent reduced-intensity chemotherapy, based on fludarabine and melphalan or treosulfan, has been proposed to reduce the toxicity of standard regimen but the gonadotoxicity remains to be investigated

Long-term treatment with hydroxyurea as well as Iron overload secondary to repeated transfusions may also negatively impact on the ovarian reserve and fertility potential of patients with haematological benign diseases

Benign gynecological diseases

- All benign conditions that involve the ovaries such as endometriosis
- ovarian cysts
- borderline tumors

may be at risk of infertility due to the disease itself

or surgical-related depletion of the ovarian reserve

Endometriosis

- Ovarian endometriomas are cysts that release potentially toxic compounds which diffuse through the cyst wall and damage the ovarian reserve .
- AMH levels are decreased in unoperated patients with endometriomas in comparison to healthy controls
- AMH levels in patients with bilateral endometriomas are lower than in patients with unilateral endometriomas

- Conflicting reports exist regarding the relation between AMH levels and endometrioma size and, thus, doubts of the relevance of endometrioma size on ovarian reserve still remain

- Existence of endometriomas alone has no effect on the clinical pregnancy and live birth rates after IVF however, the presence of deep endometriosis was associated with reduced clinical pregnancy and the live birth rates

- Endometriosis treatment and, specifically, surgical removal of the cysts has also been proven to have an important impact on ovarian reserve and function,

- Studies showing a decrease in AMH levels and
- number of oocytes responsive to ovarian stimulation
- compromised ovarian function tests
- decrease in age at menopause in women after laparoscopic stripping of endometrioma

- The relevance of pre-treatment AMH levels to predict the chance of future pregnancy or the need for fertility preservation is unclear, as studies reporting on this have made conflicting conclusions.

- For women with reduced ovarian reserve (Bologna criteria, AMH <0.5ng/ml), advise needs to be individualized and the value of FP is unclear .

Women requesting oocyte cryopreservation for age-related fertility loss

- Ovarian reserve testing should not be performed for making FP decisions.

THANKS