日本がん・生殖医療学会「日本癌治療学会の小児、思春期・若年がん患者の妊孕性温存に関する診療ガイドライン 2017 年版の性腺リスク分類に掲載されていない、妊孕性温存療法の適応疾患に関する検討委員会」（委員長：小野政徳）

令和 2 年度 厚生労働省科学研究費（がん対策推進総合研究事業）「がん・生殖医療連携ネットワークの全国展開と小児・AYA 世代がん患者に対する妊孕性温存の診療体制の均てん化に向けた臨床研究-がん医療の充実を志向して（19EA1015）」研究⑤「本邦におけるがん領域における妊孕性温存療法の均てん化に関する調査研究」（研究代表者：鈴木直）

# 日本癌治療学会の小児、思春期・若年がん患者の妊孕性温存に関する診療ガイドライン 2017 年版の性腺リスク分類に掲載されていない、妊孕性温存療法の適応疾患に関する報告（概要）

（案）

## 1. 目的

近年、全国の自治体等による小児、思春期・若年がん患者に対する妊孕性温存療法に対する公的助成金制度が構築され、日本癌治療学会の「小児、思春期・若年がん患者の妊孕性温存に関する診療ガイドライン 2017 年版」（以下、本ガイドライン）の性腺毒性のリスク分類に掲載されている妊孕性温存療法の適応のがん患者に対する妊孕性温存が普及されつつある。一方、がん・生殖医療においては、乳がんに対するホルモン療法や、再生不良性貧血や自己免疫疾患等の良性疾患（非がん疾患）に対して性腺毒性を有する治療が行われる場合が少なくない。そのため、本ガイドラインに掲載されていない治療開始前に妊孕性温存を考慮すべきがん疾患や非がん疾患の患者には助成が行き届かず、これら患者は妊孕性温存の機会を損失している。一方、本領域を先行して進めてきた海外では、がん疾患に限定することなく非がん疾患においても、治療法による性腺毒性の分類を公表し、治療法ベースの妊孕性温存に関する診療ガイドラインへのシフトも始まっている（別添資料 1、２）。

令和 3 年 4 月より開始される、国の研究事業の一環としての妊孕性温存に係る経済的支援において、治療によって妊孕性喪失が想定されるすべてのがん等患者に均等な機会が与えられるためには、本ガイドラインの性腺毒性のリスク分類に掲載されていない妊孕性温存療法の適応疾患及び治療の提示が急務となる。以上より、日本がん・生殖医療学会は、厚労科研研究班と協働で、各領域の専門家より意見を募り文献的考察および海外ガイドライン等を交えて、妊孕性温存療法が適応となる疾患等をまとめた。なお、本報告書は Minds 診療ガイドラインの手引きに準じて作成したガイドラインではなく、専門家の意見をまとめた報告書となることから、妊孕性温存療法の適応の妥当性に関して引き続き検証を続ける必要性がある。

## 2. 本ガイドラインの性腺リスク分類に掲載されていない、妊孕性温存療法の適応疾患

① 長期間の治療によって卵巣予備能の低下が想定されるがん疾患：乳がん（ホルモン療法）等

② 造血幹細胞移植が実施される非がん疾患：再生不良性貧血、遺伝性骨髄不全症候群（ファンコニ貧血等）、原発性免疫不全症候群、先天代謝異常症、サラセミア、鎌状赤血球症、慢性活動性 EB ウイルス感染症等

③ アルキル化剤が投与される非がん疾患：全身性エリテマトーデス、ループス腎炎、多発性筋炎・皮膚筋炎、ベーチェット病等

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参考：日本癌治療学会の「小児、思春期・若年がん患者の妊孕性温存に関する診療ガイドライン 2017 年版」担当領域

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**別添資料**

1. European Society for Medical Oncology (ESMO)FP ガイドライン 2020
2. aogs.13577 (Challenges of fertility preservation in non‐oncological diseases)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

別添資料 1

SPECIAL ARTICLE

# Fertility preservation and post-treatment pregnancies in post-pubertal cancer patients: ESMO Clinical Practice Guidelines†

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**Key words:** cancer, Clinical Practice Guidelines, fertility, pregnancy

## INTRODUCTION

Cancer remains a public health problem worldwide that also includes young adults.[1] Given the ongoing improvements in survival for most malignancies, a significant proportion of people affected by cancer face the consequences of treatment-related late effects, making survivorship an area of crucial importance.[2]

At the time of diagnosis, a significant proportion of young patients are concerned about the possible impact of anticancer treatments on their fertility and future chances of conception.[3,4] Failure to address these concerns may negatively influence their choices and adherence to the proposed anticancer treatments. Considering the rising trend in delaying childbearing and the higher number of patients who have not completed their family planning at the time of diagnosis, the demand for fertility preservation and information about the feasibility and safety of pregnancy following treatment completion is expected to increase.

These guidelines provide a framework for fertility preservation and post-treatment pregnancies in post-pubertal cancer patients and include new topics beyond the previous European Society for Medical Oncology (ESMO) recommendations published in 2013.[5] The specific issues faced by prepubertal patients, indications for fertility-sparing surgery and management of cancer diagnosed during pregnancy are beyond the scope of these guidelines.

## ASSESSMENT OF GONADOTOXICITY

### *Oncofertility counselling*

All cancer patients of reproductive age should receive complete oncofertility counselling as early as possible in the treatment planning process, irrespective of type and stage of disease. This should include discussion of the patients' current or future family desire, their health and prognosis, the potential impact of the disease and/or proposed anticancer treatment on their fertility and gonadal function, chances of future conception, pregnancy outcomes and offspring, as well as the need for effective contraception in the context of systemic anticancer treatment.[6] To ensure that patients fully understand the risk of treatment-related gonadotoxicity, they should be offered complete oncofertility counselling even if there is no interest in future children at the time of diagnosis.

Oncofertility counselling should be individualised based on patient/couple- and disease/treatment-related factors, with patient interest and age as well as type of treatment being the most important (Table 1). Written information and/or online resources should be provided to all patients, whenever possible, and should be documented in the

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**Table 1. Patient/couple- and disease/treatment-related factors to be considered during oncofertility counselling at the time of diagnosis**

| Patient/couple-related factors | Disease/treatment-related factors |
|---|---|
| Sex | Type of cancer (prognosis and risk of gonadal involvement by the tumour) |
| Age | Urgency of treatment |
| BMI | Type of treatment: |
| Smoking | ChT: |
| Presence of a partner | ○ Regimen |
| Medical history | ○ Dose |
| Ovarian reserve markers (female) | RT: |
| Previous treatment for infertility | ○ Location of the RT field |
| Prior treatment with potential negative impact on fertility | ○ Dose and fractionation |
| Contraindications to medical or surgical fertility preservation options | Endocrine therapy |
| Hereditary conditions | Surgery |
| | Duration of treatment |

BMI, body mass index; ChT, chemotherapy; RT, radiotherapy.

medical record.[7] It is also important to offer psychosocial support services, and ethical review may be needed regarding these difficult issues.[8]

All patients with a potential interest in fertility preservation should be referred immediately to an appropriate fertility specialist or fertility unit. Coordination of fertility preservation requires the creation of a local/regional multidisciplinary team of oncologists/haematologists and fertility specialists. Whenever possible, to optimise patient management and cost-effectiveness, a 'hub and spoke' model should be implemented, with several oncology/haematology units efficiently referring patients interested in fertility preservation to fewer, more experienced fertility units.

Considering the limited evidence available in many areas of oncofertility, patients should be encouraged to participate in clinical trials or prospective studies.

To guarantee access to fertility preservation for every cancer patient, universal insurance coverage should be implemented.

## *Gonadotoxicity of anticancer treatments*

Both the proposed anticancer therapies, as well as the type of cancer, and the overall condition of the patient may induce treatment-related gonadal failure and infertility (defined as an impairment of a person's capacity to reproduce).[9]

The risk of treatment-related azoospermia or amenorrhoea according to different anticancer treatments is summarised in Tables 2 and 3, respectively (updated from Lee et al.[10]).

**Male patients.** Male causes of infertility encompass abnormal semen parameters; anatomical, endocrine, genetic, functional or immunological abnormalities of the reproductive system; chronic illness and sexual conditions incompatible with the ability to deposit semen in the vagina.[11]

Spermatogonia are the most important target of cytotoxic treatments. The damaging effect depends on the drug concentration or the radiotherapy (RT) dose.[12] Suppression of gonadotropin release following cranial RT may also impact on spermatogenesis, although this may be corrected by exogenous gonadotropin administration.

While low doses of chemotherapy (ChT) reduce the pool of actively dividing spermatogonia, reserve spermatogonial stem cells might survive and remain able to differentiate. Treatment-related gonadotoxicity can also be caused indirectly by a depletion and impairment of Sertoli and Leydig cells.[12] The most severe damage to spermatogonia and germinal epithelium is induced by alkylating agents, platinum compounds and long-term hydroxyurea treatment.[10,13]

**Table 2. Risks of treatment-related azoospermia and infertility in male patients[a]**

| Degree of risk | Treatment type/regimen | Comments |
|---|---|---|
| High risk | **RT**<br>***Total body RT***<br>***Testicular RT***:<br>germ cells >20 Gy<br>somatic cells >30 Gy<br>**ChT**<br>***Alkylating agents*** (cyclophosphamide, ifosfamide, procarbazine, cisplatin, chlorambucil, carmustine, lomustine, melphalan, thiotepa, busulfan, mechlorethamine) with CED >5 g/m$^2$ for germ cells and 20 g/m$^2$ for somatic cells<br>***Conditioning ChT for BMT*** (busulfan and cyclophosphamide, fludarabine and melphalan) | |
| Intermediate risk | ***Alkylating agents*** (thiotepa, cisplatin <0.6 g/m$^2$, oxaliplatin, carboplatin, dacarbazine)<br>***Anthracyclines*** (doxorubicin, idarubicin, daunorubicin)<br>***Mitoxantrone***<br>***Antimetabolites*** (cytarabine, gemcitabine) | |
| Low risk | ***Antimetabolites*** (mercaptopurine, methotrexate, fludarabine)<br>***Tubulin-binding agents/vinca alkaloids*** (vincristine, vinblastine)<br>***Topoisomerase inhibitors*** (etoposide)<br>***Antitumour antibiotics*** (bleomycin, dactinomycin, mitomycin C) | |
| Unknown risk | ***Antimetabolites*** (fluorouracil, thioguanine)<br>***Taxanes*** (paclitaxel, docetaxel)<br>***Topoisomerase inhibitors*** (irinotecan, topotecan, teniposide)<br>***Immunotherapy***<br>***Targeted therapies*** (including monoclonal antibodies and small molecules) | For taxanes, only very short-term evaluation (<6 months): increased FSH, decreased inhibin B and testicular volume when evaluated just after completion of combined ChT<br>Limited evidence for imatinib (temporarily decreased sperm parameters) |

BMT, bone marrow transplantation; CED, cyclophosphamide equivalent dose; ChT, chemotherapy; FSH, follicle-stimulating hormone; RT, radiotherapy.
[a] Adapted from Lee et al.[10] Table contains examples and is not a complete list.

**Table 3. Risks of treatment-related amenorrhoea in female patients**[a]

| Degree of risk | Treatment type/regimen | Comments |
|---|---|---|
| High risk (>80%) | Haematopoietic stem cell transplantation (especially alkylating agent-based myeloablative conditioning with cyclophosphamide, busulfan, melphalan or total body RT) | |
| | EBRT >6 Gy to a field including the ovaries | |
| | 6 cycles of CMF, CEF, CAF or TAC in women of ≥40 years | Significant decline in AMH levels after treatment<br>Early menopause |
| | 6–8 cycles of escalated BEACOPP in women of ≥30 years | Significant decline in AMH levels after treatment |
| Intermediate risk (20%–80%) | 6 cycles of CMF, CEF, CAF or TAC in women of 30–39 years | Significant decline in AMH levels after treatment<br>Early menopause |
| | 4 cycles of AC in women of ≥40 years | Significant decline in AMH levels after treatment |
| | 4 cycles of AC/EC → taxane | Significant decline in AMH levels after treatment |
| | 4 cycles of dd (F)EC → dd taxane | |
| | 6–8 cycles of escalated BEACOPP in women of <30 years | Significant decline in AMH levels after treatment |
| | 6 cycles of CHOP in women of ≥35 years | Early menopause |
| | 6 cycles of DA-EPOCH in women of ≥35 years | Significant decline in AMH levels after treatment |
| | FOLFOX in women of ≥40 years | |
| Low risk (<20%) | 6 cycles of CMF, CEF, CAF or TAC in women of <30 years | Significant decline in AMH levels after treatment<br>Early menopause |
| | 4 cycles of AC in women of <40 years | Significant decline in AMH levels after treatment |
| | 2 cycles of escalated BEACOPP | Significant decline in AMH levels after treatment |
| | ABVD | Insignificant decline in AMH levels after treatment |
| | 6 cycles of CHOP in women of <35 years | Early menopause |
| | 6 cycles of DA-EPOCH in women of <35 years | Significant decline in AMH levels after treatment |
| | AML therapy (anthracycline/cytarabine) | Insignificant decline in AMH levels after treatment |
| | ALL therapy (multi-agent) | Insignificant decline in AMH levels after treatment |
| | Multi-agent ChT for osteosarcoma (doxorubicin, cisplatin, methotrexate, ifosfamide) in women of <35 years | |
| | Multi-agent ChT for Ewing's sarcoma (doxorubicin, vincristine, dactinomycin, cyclophosphamide, ifosfamide, etoposide) in women of <35 years | |
| | FOLFOX in women of ≤40 years | |
| | Antimetabolites and vinca alkaloids | |
| | BEP or EP in women of <30 years | |
| | Radioactive iodine (I-131) | Decline in AMH levels after treatment |
| | Bevacizumab | |
| Unknown risk | Platinum- and taxane-based ChT | |
| | Most targeted therapies (including monoclonal antibodies and small molecules) | |
| | Immunotherapy | |

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; AC, doxorubicin, cyclophosphamide; ALL, acute lymphoid leukaemia; AMH, anti-Müllerian hormone; AML, acute myeloid leukaemia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, procarbazine; BEP, bleomycin, etoposide, cisplatin; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ChT, chemotherapy; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DA-EPOCH; dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; dd, dose dense; EBRT, external beam radiotherapy; EC, epirubicin, cyclophosphamide; EP, etoposide, cisplatin; F, fluorouracil; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; Gy, Gray; RT, radiotherapy; TAC, docetaxel, doxorubicin, cyclophosphamide.

[a] Adapted from Lee et al.[10] Table contains examples and is not a complete list.

The germinal epithelium is highly susceptible to RT-related damage.[13] Spermatogonia are sensitive to RT, with doses as low as 0.1 Gy leading to short-term cessation of spermatogenesis. Doses of 2-3 Gy also affect spermatogonial stem cells and cause long-term azoospermia. Doses of ≥6 Gy (e.g. total body RT with 10 or 13 Gy) deplete the spermatogonial stem cell pool and cause long-term or permanent infertility. Leydig cell insufficiency and testosterone deficiency have been described with RT doses of 20-24 Gy.[13]

A potential negative impact of cancer on semen parameters has been described for patients with testicular tumours[14] and Hodgkin's lymphoma.[15]

**Female patients.** Cancer and anticancer treatments may affect post-treatment ovarian function by a reduction in ovarian reserve (i.e. the primordial follicle pool); a disturbed hormonal balance; or by anatomical or functional changes to the ovaries, uterus, cervix or vagina. Reduced ovarian function may result in infertility and premature ovarian insufficiency [POI; defined as oligo/amenorrhoea for ≥4 months and follicle-stimulating hormone (FSH) levels of >25 IU/l on two occasions, 4 weeks apart, before the age of 40 years].[16] Notably, in cancer patients, menstrual function can resume many months after completion of treatment; in addition, infertility and POI may occur despite temporary resumption of menses.[17] Ovarian reserve can be estimated by measuring serum anti-Müllerian hormone (AMH) levels (low levels represent low ovarian reserve) and/or antral follicle count.[18] However, their clinical utility, particularly in predicting future fertility and reproductive lifespan, is unclear.

ChT-related amenorrhoea is mainly due to damage to growing follicles that occurs within weeks after ChT initiation and is often transient.[19] Depending on age, pretreatment ovarian reserve and type of treatment, exhaustion of the primordial follicle pool may occur with subsequent POI. Because of their cell-cycle nonspecific mode of action, alkylating agents induce the greatest damage, not only to growing follicles but also to oocytes, resulting in a striking reduction of the primordial follicle pool.[19]

The impact of most targeted agents (including monoclonal antibodies and small molecules) and immunotherapy is largely unknown. Limited data for the anti-human epidermal growth factor receptor 2 (HER2) agents trastuzumab and/or lapatinib indicate no apparent gonadotoxicity.[20] An increased risk of ovarian dysfunction in patients treated with bevacizumab cannot be excluded.[21]

Endocrine treatments may have an indirect effect on fertility by delaying time to pregnancy. A higher risk of treatment-related amenorrhoea with the use of tamoxifen following ChT has been described in several studies.[22] Nonetheless, no impact on AMH levels has been shown.[23]

RT exposure causes a reduction in the number of ovarian follicles and has an adverse effect on uterine and endometrial function; the gonadotoxic effect of RT is dependent on the RT field, dose and fractionation schedule, with single doses more toxic than multiple fractions.[24] RT-related ovarian follicle loss already occurs at doses of <2 Gy. The effective sterilising dose at which 97.5% of patients are expected to develop immediate POI decreases with increasing age at the time of treatment, ranging from 16 Gy at 20 years to 14 Gy at 30 years.[24] RT also induces loss of uterine elasticity in a dose-dependent manner. This interferes with uterine distension, with increased risk throughout pregnancy.[25]

A potential negative impact of cancer on ovarian reserve has been described for young women with lymphoma but not for patients with other malignancies.[26]

### Recommendations

- All cancer patients of reproductive age should receive complete oncofertility counselling as early as possible in the treatment planning process, irrespective of the type and stage of disease [III, A].
- Oncofertility counselling should be individualised based on patient/couple- and disease/treatment-related factors, with patient interest and age as well as type of treatment being the most important [V, A].
- Written information and/or online resources during oncofertility counselling should be provided to patients whenever possible [V, A].
- All patients with a potential interest in fertility preservation should be referred immediately to an appropriate fertility specialist/unit [III, A].
- As there is no absolute threshold of exposure to anticancer therapies that determines gonadal failure and infertility, every patient should be considered as being at potential risk of developing treatment-related gonadotoxicity [V, A].

## FERTILITY PRESERVATION: MALE PATIENTS

A management flowchart for fertility preservation in male patients is shown in Figure 1.

### Sperm cryopreservation

Sperm cryopreservation is a widely available and standard method to preserve an individual's reproductive potential. This strategy relies on the survival and fertilisation capacity of spermatozoa after semen freezing, mostly in liquid nitrogen vapour or following controlled slow freezing.[27,28] Since the introduction of intracytoplasmic sperm injection, freezing of a single semen sample containing mature sperm may be sufficient to attempt future fatherhood.

Success using cryopreserved sperm from cancer patients shows an aggregate rate for parenthood of 49% [95% confidence interval (CI) 44%-53%].[28] Long-term storage of cryopreserved sperm does not correlate with worse outcomes or thawed semen quality.[29]

Sperm cryopreservation is indicated for adults and teenagers from Tanner pubertal stages II-III. If the patient is not able to ejaculate by masturbation, assisted ejaculation techniques such as penile vibratory stimulation or electroejaculation may be proposed.[30] In case no sperm can be found in the semen sample, conventional testicular sperm extraction (TESE) or microsurgical TESE (microTESE) might be applied to extract sperm present in the testicular tissue. Sperm cryopreservation should be offered before treatment initiation because of potential genetic abnormalities in sperm after exposure to ChT or RT.[31]

Data from longitudinal, prospective cohort studies are awaited to provide further evidence on the potential risk of congenital abnormalities.

### Gonadal shielding during RT

Gonadal shielding during total-body RT protects the germinal epithelium. Adolescent (and childhood) patients who did not have testicular shielding had a significantly smaller testicular volume in adulthood compared with those who received testicular shielding.[32] Diminished testosterone/luteinising hormone ratio was also reported without testicular shielding.

### Medical gonadoprotection

Hormone suppression treatments such as a gonadotropin-releasing hormone agonist (GnRHa), with or without androgens, antiandrogens or progestins, are not protective in male cancer patients.[33]

So far, other molecules have been tested in animals or *in vitro*, showing only partial effects, and none of them are in clinical use for this indication (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.09.006).

### Other experimental options

Information regarding other experimental options can be found in Section 1 of the supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.09.006.

### Recommendations

- Sperm cryopreservation before initiation of anticancer treatments (ChT, RT or surgery) is standard of care and should be discussed with any male cancer patient at risk of infertility [III, A].

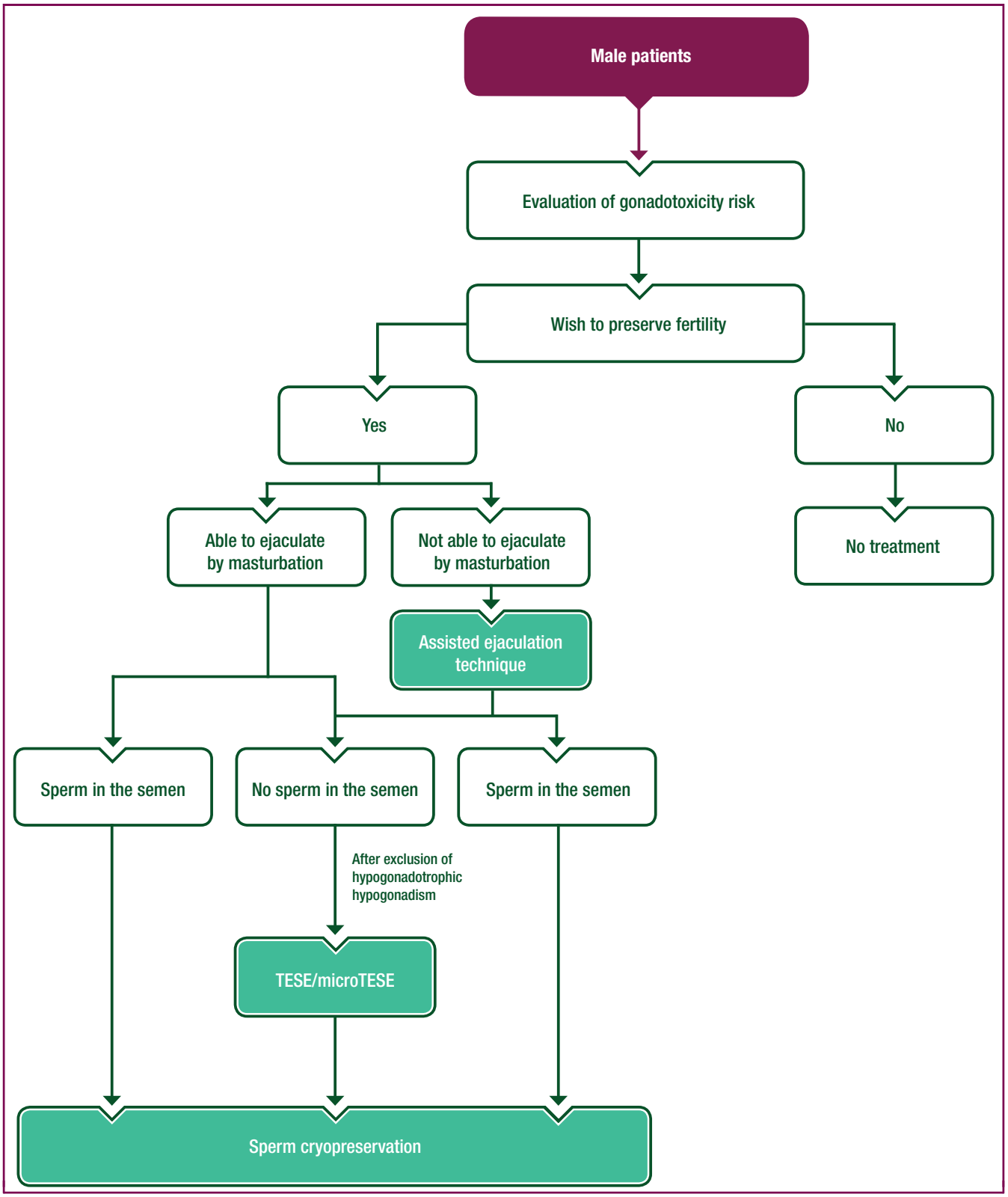


**Figure 1. Management flowchart for fertility preservation in male patients.**
microTESE, microsurgical testicular sperm extraction; TESE, testicular sperm extraction.

- To reduce the risk of infertility, reducing RT exposure by shielding or removing the testes from the radiation field should be applied whenever possible [IV, A].
- Medical gonadoprotection (GnRHa with or without androgens, antiandrogens or progestins) should not be offered for fertility preservation in male cancer patients [III, D].

## FERTILITY PRESERVATION: FEMALE PATIENTS

A management flowchart for ovarian function and/or fertility preservation in female patients is shown in Figure 2.

### *Oocyte and embryo cryopreservation*

Oocytes and embryos can be safely and efficiently cryopreserved before the initiation of anticancer treatments. While embryo cryopreservation is an established and reproducible technology, it requires the use of sperm and the presence of a partner or donor. Conversely, oocyte cryopreservation can be carried out without a partner and so it is the preferred option for most post-pubertal women. The ability to cryopreserve oocytes has become much more successful in recent years since the development of ultra-rapid freezing (vitrification).[34]

For oocyte and embryo cryopreservation, ~2 weeks of ovarian stimulation with gonadotropins is required, followed by follicle aspiration. Ovarian stimulation can be started at any time of the menstrual cycle ('random start stimulation').[35] Developments in ovarian stimulation protocols allow more rapid completion of the process than previously, without affecting their efficacy. However, timing is a crucial factor as the procedure must be completed before initiation of any ChT. In women with a low ovarian reserve and without an urgent need to initiate anticancer treatments, double stimulation can be considered; this requires 4 weeks of treatment and approximately doubles the number of oocytes retrieved.[36]

The efficacy of oocyte and embryo cryopreservation to generate a subsequent pregnancy is tightly connected to the number of mature oocytes retrieved after ovarian stimulation. The number of retrieved oocytes is reduced in women with poor ovarian reserve (i.e. low AMH level due to ovarian surgery or age). The number of collected oocytes is age dependent, varying from 15.4 ± 8.8 in women <26 years of age to 9.9 ± 8.0 in women 36-40 years of age.[37] Recent data reported a cumulative live birth rate of 61.9% if 12 oocytes were cryopreserved in women ≤35 years of age and 43.4% if 10 oocytes were cryopreserved in women >35 years of age.[38] While some studies have reported that the number of recovered oocytes in women with cancer is not reduced,[37] others have found a reduction (particularly in lymphoma patients), with reduced fertilisation and implantation rates, resulting in a lower live birth rate compared with a noncancer population.[38]

Ovarian stimulation can lead to side-effects caused by the medication as well as complications during the oocyte pick-up, including bleeding from the ovary and pelvic infection. Severe ovarian hyperstimulation syndrome, clinically relevant bleeding or inflammation/infections after follicular aspiration in women with normal haematopoiesis are rare in the general infertility population and in cancer patients.[39,40] An increased risk of bleeding or infection may be present in women with impaired haematopoiesis (i.e. neutropenic or with low platelet count), such as those with some haematological malignancies, and should be taken into account. In estrogen-sensitive tumours, reduction of estradiol concentration is recommended during ovarian stimulation and can be achieved by co-treatment with aromatase inhibitors (e.g. letrozole 2 × 2.5 mg/day), which reduces estrogen serum concentration by more than 50%.[41] The use of letrozole does not reduce the number of mature oocytes obtained or their fertilisation capacity; in addition, no effect on congenital abnormality rates in children has been observed.[42] Tamoxifen can also be used to antagonise the effects of high estrogen levels but data are less robust.[43] Although numbers remain small, there is no evidence that ovarian stimulation for fertility preservation has an adverse effect on survival in women with breast cancer[43] or other malignancies.[44]

It has been proposed that ovarian stimulation can be combined with cryopreservation of ovarian tissue to increase the success rate in women receiving highly gonadotoxic treatments.[45] Half of an ovary is removed laparoscopically and ovarian stimulation is started 1-2 days later. Although data are very limited, the number of oocytes obtained does not appear to be significantly reduced after removal of ovarian tissue. The time required for the combination of both treatments is ~2.5 weeks.[45]

Oocyte or embryo cryopreservation is indicated for women preferably ≤40 years of age who will be exposed to gonadotoxic anticancer therapies and who want to preserve their fertility. It is not indicated in women with serious coagulation defects or high risk of infections. Transabdominal monitoring and oocyte recovery may be possible in those for whom vaginal procedures are not possible or acceptable. Women choosing to store embryos created with their partner's sperm should be advised that the embryos will be the joint property of the couple; in the event of the relationship not continuing, there may be issues in using the embryos. An established collaboration between oncology and fertility units is crucial.

There is a need for data on all aspects of oocyte cryopreservation from larger series of women to clarify whether certain diagnoses may benefit from particular stimulation protocols, the effects on oocyte quality and most importantly, cumulative live birth rates. Future studies are also needed to investigate the benefits of combining different fertility-preservation methods to increase pregnancy rates.

### *Ovarian tissue cryopreservation*

Ovarian tissue cryopreservation is an alternative approach for preserving fertility before gonadotoxic treatments.[46,47] While it is still regarded as experimental in some countries, the American Society for Reproductive Medicine suggests that it should be considered as an established procedure to be offered to carefully selected patients.[48]

Biopsies of the ovarian cortex or unilateral ovariectomy are usually carried out by laparoscopy under general anaesthesia. No pretreatment is required so the process can be carried out in a short timeframe and ChT started the following day, if required. Although vitrification is quicker and less expensive,

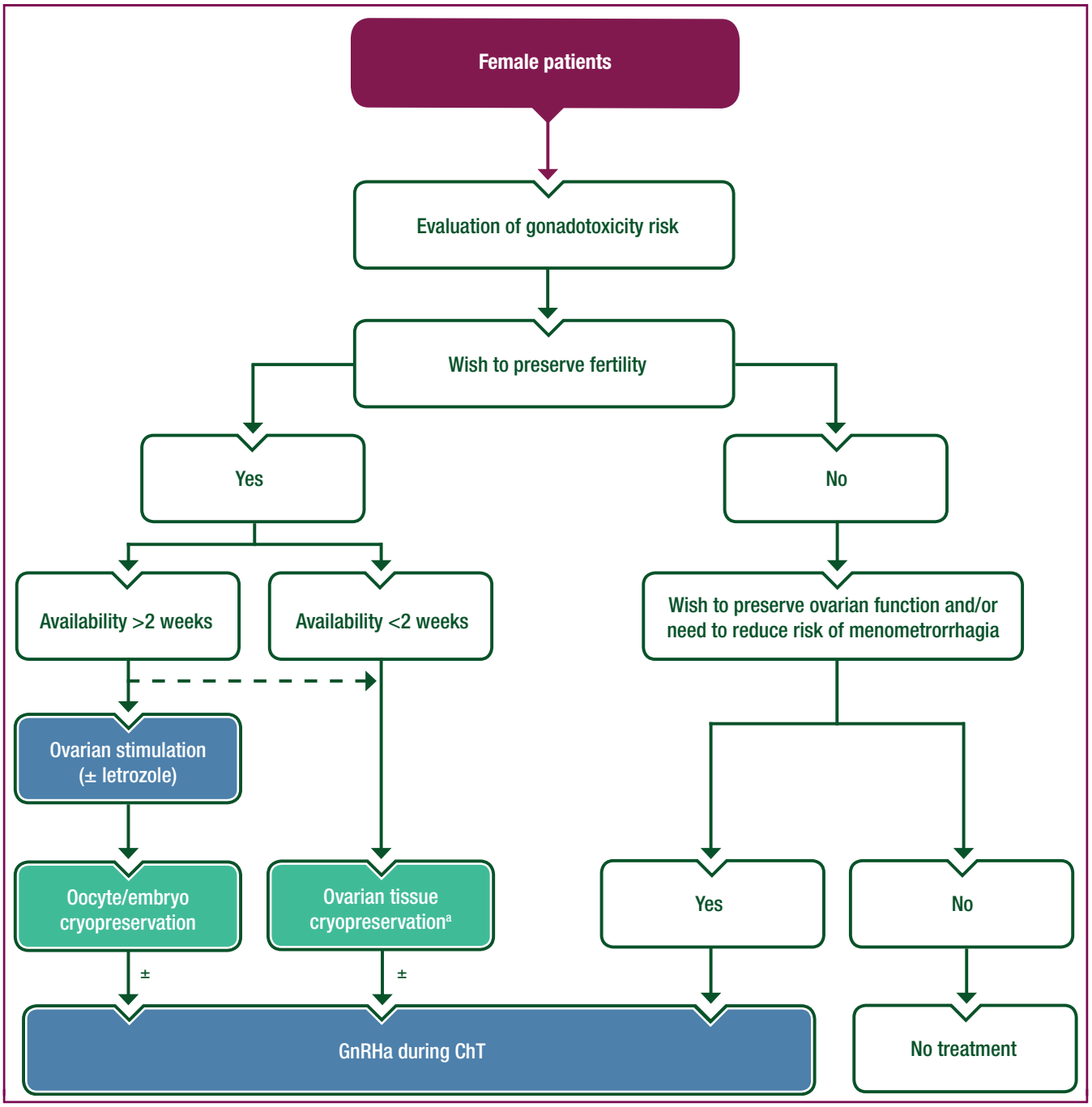


**Figure 2. Management flowchart for ovarian function and/or fertility preservation in female patients.**
ChT, chemotherapy; GnRHa, gonadotropin-releasing hormone agonist.
[a]To be offered preferably in women ≤36 years of age and to be considered with particular caution in cases of acute leukaemia, or any solid tumour or haematological disease with pelvic involvement.

slow freezing remains the standard of care because almost all pregnancies achieved after transplantation have been obtained using this procedure.[49] Ovarian tissue cryopreservation should be offered only in laboratories with specific expertise and facilities to support safe tissue cryopreservation and storage for subsequent autologous transplantation, with necessary regulation. The 'hub and spoke' model, with ovarian surgery carried out locally and tissue transported to a central laboratory, may be preferred.

Transplantation, either orthotopic or heterotopic, is currently the only method available in clinical practice to restore ovarian function and fertility using cryopreserved ovarian tissue. More than 300 women worldwide have undergone the procedure and ovarian function restoration was achieved in 95% of cases within 4-9 months.[49] To date, more than 180 babies have been born using this procedure. Approximately 85% of the women receiving ovarian transplants were cancer survivors. The live birth rate per patient

was ~40%, half of which were from natural conceptions, thus avoiding the need for further medical intervention.[49] As with oocyte and embryo cryopreservation, the main factor affecting success rate is age: women of younger age at ovarian tissue cryopreservation have better fertility outcomes after ovarian tissue transplantation than older women, with only a few pregnancies achieved in women over 36 years of age.[50]

Ovarian tissue collection and transplantation are usually carried out by laparoscopy. Surgical risk is considered low and complications (e.g. conversion laparotomy, bleeding, reintervention for cutaneous infection, bladder lesion or minor complications) are rare (0.2%-1.4%).[51] The procedure should not be proposed to patients with high surgical/anaesthesia risks related to their disease and ideally should be done at the same time as other procedures that require anaesthesia. The risk of disease transmission during transplantation due to residual neoplastic cells within the ovarian cortex is one of the major safety concerns, especially in pelvic cancers or systemic diseases such as leukaemia. Several diseases at advanced stages, such as Burkitt's lymphoma, non-Hodgkin's lymphoma, breast cancer and sarcoma, might also carry a risk of ovarian involvement.[52] In a recent review, 9 out of 230 cancer patients who underwent ovarian tissue transplantation experienced recurrence of their disease but none were related to the transplantation procedure.[49] Nevertheless, ovarian tissue should always be carefully analysed before grafting using all available technologies, such as immunohistochemistry and molecular markers, according to the disease. Xenografting has also been used in this context. Data on children are reassuring as no congenital malformations have been reported.

Ovarian tissue cryopreservation is appropriate when the time available before starting anticancer treatments is too short for ovarian stimulation and oocyte or embryo cryopreservation. Although there is no clear consensus on the maximum age for ovarian tissue cryopreservation, it is usually recommended to offer this procedure only to women $\leq$36 years of age.[50,53] Ovarian tissue cryopreservation can also be carried out after an initial, low-intensity gonadotoxic treatment regimen in order to reduce the risk of neoplastic cells being present in the ovary (i.e. in leukaemia patients) or when the patient's initial health condition contraindicates an immediate procedure.[54] Although the procedure has recently been carried out with success in a patient affected by acute myeloid leukaemia,[55] the risk of tissue contamination remains a major concern in such patients and there is a need for very careful evaluation in each individual case. While normal oocytes can develop from cryopreserved ovarian tissue after ChT administration, there are no robust data regarding the impact of different regimens and time interval between last treatment dose and ovarian tissue cryopreservation on the subsequent reproductive outcomes. The ischaemic process after transplantation of ovarian cortex induces major follicular loss, reducing the lifespan of graft function. Restoration of ovarian function after grafting occurs in most women, but is very variable in duration, lasting from just a few months to several years in some cases. For some women, two or three graft procedures are required to achieve a pregnancy.[49]

Research is ongoing to improve tissue function after grafting using several tools, including human adipose tissue-derived stem cells, mesenchymal stem cells and decellularised scaffolds.

### *Ovarian transposition and gonadal shielding during RT*

Two options exist for protecting ovaries from RT: transposition of the ovaries before RT and gonadal shielding during RT.

Ovarian transposition outside the planned RT field is a routinely used technique to minimise ovarian follicle RT exposure. Although both laparotomic and laparoscopic approaches are possible, the procedure is mostly carried out by laparoscopy to accelerate recovery and avoid postponing RT.[56] The ovary is mobilised with its vascular pedicle and the location is marked with radio-opaque clips to allow identification of the transposed ovary. It is possible to transpose only one ovary, but better results are achieved with a bilateral procedure. Transposition of the ovary into subcutaneous tissue is another option but it is associated with a higher risk of cyst formation.[56] Transposed ovaries can be safely punctured for oocyte retrieval.[57] In certain cases, ovaries can be returned to their original location after RT. The rate of retained ovarian function is approximately 65% in patients undergoing surgery and RT.[58] Reasons for failure include necrosis related to vascular impairment and migration after insufficient fixation. Success rate is influenced by the method of evaluation (presence of menstrual cycle, FSH levels, AMH levels) and the duration of follow-up (as ovarian function decreases over time). Very few data are available for pregnancy rates, which seem to vary between 0% and 50%, and these rates are also dependent on the target irradiated organ.[56] The surgical risk of ovarian transposition is similar to other gynaecological procedures (i.e. risk of bowel and vessel injury). Risk of developing ovarian carcinoma in a transposed ovary is extremely low.[58] This could be reduced even further when fallopian tubes are resected during the surgical procedure.

Gonadal shielding during RT by lead blocks reduces the expected RT dose to 4-5 Gy.[59] The minimum free margin should be 2 cm in order to reduce the risk of gonadal irradiation due to inner organ movement.

Ovarian transposition and gonadal shielding are indicated in women $\leq$40 years of age who are scheduled to receive pelvic RT for cervical (if there is a low risk of ovarian metastasis or recurrence), vaginal, rectal or anal cancers, Hodgkin's or non-Hodgkin's lymphoma in the pelvis or Ewing's sarcoma of the pelvis.

Long-term follow-up evaluating the risks of transposition and fertility rates after RT completion is needed.

### *Medical gonadoprotection*

The aim of medical gonadoprotection during ChT is to reduce the risk of POI and its associated fertility and endocrine-related consequences. Therefore, this strategy

may also be of value in patients without a desire for pregnancy and not interested in fertility preservation. Potential advantages are its suitability for premenopausal patients of all ages, non-invasive nature, low health risk and possible use in conjunction with fertility-preservation strategies.[60] The potential disadvantages of medical gonadoprotection are the possible interference with anticancer therapies, risk of damaging the oocytes and the need for administering these agents before and during anticancer treatment.[60]

Temporary ovarian suppression during ChT achieved by administering a GnRHa (starting at least 1 week before the initiation of systemic cytotoxic therapy and continued for the duration of therapy) is the only strategy that has entered clinical use. Several potential new methods of medical gonadoprotection with hormonal and non-hormonal agents are currently under investigation (supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.09.006).[19]

In cancer patients, most of the available randomised trials assessing the use of GnRHa during ChT have been conducted in premenopausal breast cancer patients, but evidence also exists in women with haematological malignancies; there are limited data to counsel cancer patients diagnosed with other solid tumours. Notably, in most of the trials, the primary end point was POI (defined as amenorrhoea at different time points following ChT completion, with few trials using composite end points of amenorrhoea and postmenopausal hormonal levels). A small number of studies reported on post-treatment pregnancies.

In premenopausal breast cancer patients, 14 randomised trials investigated the efficacy of this strategy: all but four studies showed a statistically significant reduction in POI risk with concurrent administration of a GnRHa during systemic cytotoxic therapy.[61] In an individual patient-level meta-analysis including the five major breast cancer trials ($N = 873$), the administration of a GnRHa during ChT was associated with a significant reduction in POI rates [from 30.9% to 14.1%; adjusted odds ratio (OR) 0.38; 95% CI 0.26-0.57; $P < 0.001$] and a higher number of post-treatment pregnancies [37 versus 20; incidence rate ratio (IRR) 1.83; 95% CI 1.06-3.15].[62] Treatment effect in reducing POI risk was observed in both patients with hormone receptor-positive and -negative disease and was irrespective of patient age at the time of treatment, type and duration of ChT.[62]

In premenopausal women with haematological malignancies, four randomised trials investigated the efficacy of this strategy but none showed a protective effect with the use of a GnRHa during ChT.[61] A recent meta-analysis included three trials ($N = 109$ patients) and showed no significant difference in POI rates [18.9% versus 32.1%; risk ratio (RR) 0.70; 95% CI 0.20-2.47] or post-treatment pregnancies (17 versus 18; RR 1.13; 95% CI 0.66-1.93) between patients that received ChT alone and those with concurrent GnRHa administration.[63]

In premenopausal women with other solid tumours, only one randomised trial including 30 patients with ovarian cancer is available.[64] A significant reduction in POI rates (from 33.3% to 0.0%; $P = 0.02$) was observed with the use of a GnRHa during ChT; no data on post-treatment pregnancies were reported.

In terms of safety, concurrent use of a GnRHa during ChT is associated with a higher incidence of menopausal symptoms (mainly hot flushes and sweating) that are of low severity grade in the majority of cases and are reversible.[62] In women with hormone receptor-positive breast cancer, concurrent administration of a GnRHa during ChT is not associated with detrimental survival outcomes;[62,65] subsequent ovarian function suppression should be considered as part of the adjuvant endocrine treatment in these patients.[66]

Based on the available evidence, temporary ovarian suppression with a GnRHa during ChT should be considered a standard option for ovarian function preservation in premenopausal breast cancer patients undergoing (neo)adjuvant systemic cytotoxic therapy. In premenopausal women with other malignancies who are candidates to receive ChT, despite the limited available data, use of a GnRHa may be discussed considering its other potential medical effects, including menstrual cycle control and prevention of menometrorrhagia risk. Importantly, for patients interested in fertility preservation, temporary ovarian suppression with a GnRHa during ChT should not be considered as an alternative to cryopreservation techniques. In this setting, a GnRHa can be offered but only following cryopreservation procedures or when these surgical options are not accessible (for logistical, timing, cost or personal ethical reasons).

Further research efforts are needed to collect long-term follow-up data (including post-treatment pregnancies and age at menopause) from existing randomised trials. Prospective studies are warranted to better investigate the protective gonadal effect of a GnRHa during ChT using more sensitive markers of ovarian reserve, including AMH levels and antral follicle count.

### *Other experimental options*

Information regarding other experimental options for female fertility preservation can be found in Section 2 of the supplementary Material, available at https://doi.org/10.1016/j.annonc.2020.09.006.

### *Recommendations*

- When a 2-week treatment delay is feasible, oocytes or embryos can be safely and efficiently cryopreserved before the initiation of anticancer therapies [III, A].
- Close links with reproductive medicine centres are required to allow timely referral for counselling and access to oocyte and embryo cryopreservation [V, A].
- Random start ovarian stimulation protocols should be applied to limit the delay in starting anticancer treatments [III, A].
- As age is a major determinant of the likelihood of success, women should be clearly advised of their age-related chance of achieving a successful pregnancy [III, A].

- Aromatase inhibitors can be given to prevent supraphysiological estrogen concentrations during ovarian stimulation in women with estrogen-sensitive tumours [III, C].
- Ovarian tissue cryopreservation is an alternative procedure when oocyte or embryo cryopreservation are not feasible [III, A] with the following considerations:
  - Ovarian tissue cryopreservation should not be offered to older women: current evidence supports 36 years as an age limit [III, B].
  - Fragments of ovarian tissue (medulla and/or cortex) should always be analysed for the presence of neoplastic cells with appropriate techniques before transplantation [III, A]. Transplantation should be considered with particular caution in cases of acute leukaemia, or any solid tumour or haematological disease with pelvic involvement [III, A].
  - Ovarian tissue cryopreservation can be carried out after exposure to induction or a few low-intensity gonadotoxic ChT cycles [IV, B]. This approach might be of interest in patients with systemic diseases, such as leukaemia, to reduce the risk of transplanting residual malignant cells that were within the ovary before cryopreservation [V, C].
- Ovarian transposition should be considered in order to try to preserve ovarian function in women $\leq$40 years of age with an indication for pelvic RT [IV, A].
- Ovarian transposition should be carried out by experienced laparoscopists to minimise complications and maximise the chances of ovarian function preservation [IV, A].
- Gonadal shielding may be an alternative strategy to ovarian transposition, not requiring a surgical intervention [IV, C].
- For premenopausal breast cancer patients undergoing (neo)adjuvant ChT, temporary ovarian suppression with a GnRHa is recommended for ovarian function preservation, irrespective of tumour subtype [I, A].
- For premenopausal women with malignancies other than breast cancer, temporary ovarian suppression with a GnRHa during ChT may be considered as an option to potentially reduce POI risk and menometrorrhagia, but the limited and controversial evidence should be discussed with the patient [II, C].
- For young cancer patients interested in fertility preservation, temporary ovarian suppression with a GnRHa during ChT should not be considered as an alternative to oocyte or embryo cryopreservation, but it may be offered as an additional option following cryopreservation strategies or when they are not accessible [V, C].

## POST-TREATMENT PREGNANCIES IN CANCER SURVIVORS

At the time of diagnosis, a significant proportion of post-pubertal patients have not completed their family planning and express a desire for pregnancy after treatment.[3] Nevertheless, male and female cancer survivors have significantly reduced chances of post-treatment pregnancies compared with the general population.[67] Post-treatment pregnancy rates are highly dependent on the type of cancer, with the lowest rates reported for men with a history of acute leukaemia or non-Hodgkin's lymphoma and for women with a history of breast or cervical cancer.

When counselling adult cancer survivors inquiring into the feasibility and safety of post-treatment pregnancies, both patient/couple- and disease/treatment-related factors should be taken into consideration (Table 4). The potential negative influence of prior exposure to anticancer treatments on the occurrence of congenital abnormalities or obstetric and birth complications, and the possibility that a pregnancy might have a detrimental prognostic effect for the patient, particularly in the case of hormone-driven tumours, are two major concerns shared by both adult cancer survivors and their treating physicians.

While no difference has been shown for female partners of male cancer survivors,[68] there is an increased risk of developing obstetric and birth complications for female cancer survivors in terms of increased risk of prematurity (RR 1.56; 95% CI 1.37-1.77), low birth weight (RR 1.47; 95% CI 1.24-1.73), elective (RR 1.38; 95% CI 1.13-1.70) and emergency caesarean section (RR 1.22; 95% CI 1.15-1.30), assisted vaginal delivery (RR 1.10; 95% CI 1.02-1.18) and postpartum haemorrhage (RR 1.18; 95% CI 1.02-1.36).[69] The risk of these complications appears to be higher when the interval between the end of treatment and conception is short.[70] Therefore, close monitoring of post-treatment pregnancies and an interval of at least 1 year following completion of ChT is recommended in cancer survivors. In patients receiving other anticancer treatments, a specific wash-out period should be considered before conception (e.g. 3 months for tamoxifen[71] and 7 months for the anti-HER2 monoclonal antibody trastuzumab[72]).

Neonatal outcomes of pregnancies in men or women with prior exposure to anticancer treatments appear to be comparable to those of the general population. Although the literature is controversial and relies on register-based studies, a slightly increased risk of congenital

**Table 4. Patient/couple- and disease/treatment-related factors to be considered during the counselling of post-pubertal cancer survivors inquiring into the feasibility and safety of post-treatment pregnancies**

| Patient/couple-related factors | Disease/treatment-related factors |
|---|---|
| Sex | Type of cancer (prognosis and biology) |
| Age | Type, dose and duration of prior treatment (ChT, RT, endocrine therapy, surgery) |
| Personal status | Interval since treatment completion |
| BMI | Need for additional treatment |
| Smoking | Potential risk associated with treatment interruption |
| Presence of a partner | |
| Medical history | |
| Previous treatment for infertility | |
| Prior treatment with potential negative impact on fertility | |
| Prior access to fertility-preservation options | |
| Contraindications to pregnancy | |
| Hereditary conditions | |

BMI, body mass index; ChT, chemotherapy; RT, radiotherapy.

abnormalities has been reported in offspring of male cancer survivors (3.7% versus 3.2%; RR 1.17; 95% CI 1.05-1.31) when either cryopreserved sperm or fresh post-treatment sperm was used.[73] A slightly increased risk of congenital anomalies has also been described in female patients (RR 1.10; 95% CI 1.02-1.20) but this was interpreted as an artefact of the analysis.[69]

A growing amount of data (derived mostly from retrospective studies) supports the safety of conceiving following adequate treatment and follow-up of patients with breast cancer,[74] including those with prior estrogen receptor-positive disease.[75] Abortion, time to pregnancy and breastfeeding do not appear to have any impact on patient outcomes.[75] In young women with a history of hormone receptor-positive breast cancer who are candidates for 5-10 years of adjuvant endocrine therapy, no reliable data are available to counsel women on the safety of a temporary treatment interruption to have a pregnancy. In women who consider this option, patient wishes (and partner, if appropriate), age, availability of cryopreserved gametes and individual risk of recurrence are of paramount importance to be discussed. Following delivery, adjuvant endocrine therapy should be resumed to complete the recommended 5-10 years of treatment. The international, multicentre, prospective POSITIVE trial (ClinicalTrial.gov: NCT02308085) will shed light on the safety of a temporary treatment interruption to have a pregnancy in patients with prior estrogen receptor-positive disease.

The feasibility and safety of using assisted reproductive technology (ART) following anticancer treatment is an important issue to be considered for adult cancer survivors who did not have access to fertility preservation strategies at the time of diagnosis and/or where there are difficulties with spontaneous conception. Female adult cancer survivors have a higher likelihood of undergoing fertility treatments compared with healthy women, with increasing use over time.[76] In terms of efficacy, significantly lower live birth rates with the use of autologous oocytes were described for cancer survivors compared with healthy women (24.7% versus 47.7%).[77] A major impact of cancer type was shown, with the lowest live birth rates observed among breast cancer patients (14.3%) and the highest in those with a prior history of melanoma (53.5%). Conversely, in women using donor oocytes, no significant difference was observed in live birth rates between cancer survivors and healthy women (60.4% versus 64.5%), irrespective of cancer type.[77] These results further reinforce the recommendation to refer patients interested in pursuing fertility preservation strategies before the initiation of anticancer treatment. In women with hormone-driven cancers, such as survivors of hormone receptor-positive breast cancer, an additional concern is the potential detrimental effect of ART on survival outcomes. While the available safety data are reassuring for ART at the time of diagnosis when followed by the use of systemic anticancer therapies, data are limited to counsel breast cancer survivors about the safety of using ART during oncological follow-up, particularly when ovarian stimulation is needed.[78] Although there is no apparent detrimental prognostic effect, evidence is limited to draw solid conclusions in this setting and more research is needed.

### *Recommendations*

- Patient/couple- and disease/treatment-related factors should be considered when counselling adult cancer survivors regarding the feasibility and safety of post-treatment pregnancies [V, A].
- After adequate treatment and follow-up, having a pregnancy in cancer survivors should not be discouraged for safety reasons, even among women with a prior history of hormone receptor-positive breast cancer [IV, B].
- Post-treatment pregnancies in adult women with a prior history of cancer should be monitored more closely due to the potential increased risk of developing obstetric and birth complications [IV, B].
- Breastfeeding can be considered in cancer survivors who are not under active treatment [IV, B].
- Fertility preservation strategies should preferably be used at the time of diagnosis before treatment initiation [III, A].
- Where appropriate and allowed by local regulations, oocyte donation can be considered as an option in cancer survivors [IV, C].

## FERTILITY AND POST-TREATMENT PREGNANCIES IN POST-PUBERTAL PATIENTS WITH HEREDITARY CANCER SYNDROMES

Hereditary cancer syndromes are often associated with a significantly increased risk of developing early onset cancer. Several hereditary cancer syndromes are characterised by an increased chance of gynaecological cancers, including ovarian and endometrial neoplasms (supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.09.006). The identification of an inherited deleterious pathogenic variant in one of these genes plays a significant role both in cancer management and in screening, prevention and risk-reducing measures, with the subsequent impact on the patient's reproductive potential. As testing becomes more widespread, including the use of multigene panels, increased attention to fertility and pregnancy-related issues in post-pubertal patients with hereditary cancer syndromes is necessary. For some of these syndromes, the recommendation to pursue risk-reducing gynaecological surgery at a young age leads to a particularly narrow window for fertility and pregnancy. As recommended by current guidelines, all women harbouring a predisposing pathogenic variant should be encouraged to complete childbearing before planned risk-reducing gynaecological surgery.[79] At present, the recommended risk-reducing measure for women at increased risk of ovarian cancer is bilateral salpingo-oophorectomy. Of note, there is an increasing body of evidence suggesting that epithelial ovarian cancers originate in the fimbria or fallopian tubes.[80] Although risk-reducing salpingectomy alone cannot be

recommended at present outside of a clinical trial, if data emerge to support the safety of this approach, this will favourably impact reproductive issues and fertility options for these patients.

Preclinical data suggest a potential negative impact of harbouring a germline pathogenic variant in genes involved in DNA repair mechanisms on female fertility in terms of decreasing ovarian reserve, increasing fertility-related issues and POI that can lead to infertility and premature menopause.[81] Controversial data have been reported on the potential tendency for reduced ovarian reserve at diagnosis and before commencement of anticancer treatments in *BRCA*-mutated breast cancer patients.[81] To date, the potential concerns about an increased risk of gonadotoxicity in patients with hereditary cancer syndromes have not been supported by the (albeit limited) available evidence.[82,83]

Clinical data on how to optimally counsel patients with hereditary cancer syndromes facing fertility and pregnancy-related concerns remain limited. Overall, similar recommendations on fertility preservation and post-treatment pregnancies for women without germline predisposing pathogenic variants apply to patients with hereditary cancer syndromes, including the need for appropriate oncofertility counselling at the time of diagnosis. However, specific considerations should be made regarding fertility preservation, particularly for women with predisposing pathogenic variants associated with an increased risk of ovarian cancer.

Sperm cryopreservation in men and oocyte or embryo cryopreservation in women are the preferred options to be offered to newly diagnosed patients with hereditary cancer syndromes interested in fertility preservation. Importantly, these techniques facilitate the use of preimplantation genetic diagnosis (PGD) for patients who are interested in this option. Controversial data have been reported on the tendency towards a reduced response to controlled ovarian stimulation in *BRCA*-mutated breast cancer patients.[84,85]

In women with hereditary cancer syndromes that are associated with an increased risk of gynaecological malignancy and who are candidates for risk-reducing gynaecological surgery, ovarian tissue cryopreservation and temporary ovarian suppression with a GnRHa during ChT may be considered as supplementary measures to oocyte or embryo cryopreservation. Of note, a genetic test result is often not available for patients at the time of diagnosis and during oncofertility counselling, but it should be known before transplantation of cryopreserved tissue. There are limited data available to counsel patients with hereditary cancer syndromes on the efficacy and safety of these approaches,[86,87] with one concern being transplanting ovarian tissue that may harbour premalignant changes. Acknowledging the limited evidence in this regard, for patients with hereditary cancer syndromes, the choice of the transplantation site, such as directly into the remaining gonads, is crucial to ensure that all ovarian tissue can be removed after the completion of reproductive plans at the time of risk-reducing gynaecological surgery.

Available data suggest that post-treatment pregnancies are feasible among *BRCA*-mutated breast cancer patients, with no detrimental prognostic effect and no increased risk of congenital abnormalities or obstetric or birth complications.[88] Although there is a lack of evidence for patients with pathogenic variants other than *BRCA*, there are no plausible reasons to anticipate different safety considerations for post-treatment pregnancies between cancer survivors with or without hereditary cancer syndromes.

An important concern among patients with a hereditary cancer syndrome is the 50% risk of transmitting the mutated gene to their children.[89] Patients (both male and female) with a hereditary cancer syndrome, particularly those harbouring a high penetrance pathogenic variant, planning to conceive should be made aware of the options of prenatal diagnosis (via chorionic-villous or amniotic fluid sampling in week 11-20 of gestation) and PGD. The risks and benefits of both approaches need to be carefully outlined, and the need for *in vitro* fertilisation (IVF), irrespective of fertility status, if PGD is chosen must be clearly stated. A multitude of factors, including religious, cultural, ethical and socioeconomic factors can influence an individual's choice to utilise prenatal diagnosis or PGD, and any decisions should be respected. An increased awareness is needed to ensure adequate discussions on this topic, with interested patients referred to relevant experts and centres. It is worth noting, however, that these technologies are not available in all countries/centres.

Further research efforts to improve our understanding of the role of predisposing genes on patients' reproductive potential and subsequent risk of treatment-related gonadotoxicity, as well as to investigate the efficacy and safety of fertility-preservation strategies in patients with hereditary cancer syndromes, should be considered a research priority.

### *Recommendations*

- Sperm cryopreservation and oocyte or embryo cryopreservation are the preferred options and should be proposed to newly diagnosed patients with hereditary cancer syndromes interested in fertility preservation [IV, A].
- Ovarian tissue cryopreservation and temporary ovarian suppression with a GnRHa during ChT may be considered with caution in women with hereditary cancer syndromes diagnosed several years before the recommended age of risk-reducing gynaecological surgery [IV, C].
- Post-treatment pregnancies in *BRCA*-mutated breast cancer survivors should not be discouraged [IV, B]. Although no data are available for patients with pathogenic variants other than *BRCA*, there are no plausible reasons to anticipate different safety considerations for post-treatment pregnancies between cancer survivors with or without hereditary cancer syndromes [V, B].
- Patients with hereditary cancer syndromes should be informed of the possibility to undergo prenatal diagnosis (in the case of natural conception) or PGD (in the case of IVF procedures) [III, A].

## METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.09.006.[90] Statements without grading were considered justified standard clinical practice by the experts.

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別添資料 2

REVIEW

# Challenges of fertility preservation in non-oncological diseases

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## Abstract

Clinicians should provide fertility counseling to all patients receiving gonadotoxic treatment. International scientific societies have mainly focused on oncological patients, and fewer efforts have been made to apply these recommendations to women diagnosed with benign disease (eg benign hematological diseases, autoimmune diseases, and gynecological or genetic disorders). However, these indications account for 8%-13% of the demand for fertility preservation. The risk of premature ovarian failure due to treatment, or to the disease itself, can be considered fairly high for many young women. Counseling and adequate management of these women require particular attention due to the severe health conditions that are associated with some of these diseases. In this review, we address specific issues related to providing adequate fertility counseling and management for women who have been diagnosed with the major non-oncological indications, based on the literature and on our clinical experience.

KEYWORDS

autoimmune disease, benign diseases, fertility counseling, fertility preservation, genetic disorder, gynecological disorder, hematological disease

## 1 | INTRODUCTION

Fertility counseling is currently part of best practice recommendations for women at high risk of infertility or premature ovarian insufficiency (POI).[1] Infertility risk and the possibility of fertility preservation should be addressed when the intrinsic effect of a pathology or its treatment puts fertility at stake. Although the main population at risk consists of young oncology patients treated with chemotherapy, radiotherapy, or ovarian surgery, benign pathologies account for 8%-13% of the indications for fertility preservation.[2-4] Similar figures can be found in our center (Figure 1). These non-oncological indications primarily include immunological, gynecological, hematological, or genetic pathologies.[5] Ovarian failure can be induced either by the pathology itself (genetic disorders, autoimmune pathologies, inflammatory or intrinsic disorders), or by medical (eg immunosuppression using cyclophosphamide) or surgical treatments involving the ovaries. The fertility-preserving procedures used in this setting are identical to those proposed in the oncological setting and include oocyte or embryo vitrification, ovarian tissue cryopreservation, and pharmacological gonadic protection with gonadotropin-releasing hormone agonists. However, these women require particular attention and specific management.

At Erasme Hospital, in the period between August 2000 and March 2018, 11.6% and 42.4% of ovarian tissue cryopreservation indications were offered to women with benign diseases during adulthood and childhood, respectively. The main pediatric indication is the conditioning regimen for hematopoietic stem cell transplantation (HSCT) in benign hematological pathologies. Finally, although benign, some pathologies—particularly autoimmune diseases—may be associated with severe vascular damage causing renal, pulmonary, or cardiac morbidity that must be taken into account when counseling on fertility preservation procedures. In this review, we address the main indications and challenges for fertility preservation in non-oncological pathologies.

**Abbreviations:** AMH, antimüllerian hormone; HSCT, hematopoietic stem cell transplantation; POI, premature ovarian insufficiency; RIC, reduced-intensity chemotherapy; SLE, systemic lupus erythematosus.

## 2 | BENIGN HEMATOLOGICAL DISEASES

Conditioning chemotherapy regimens associated with HSCT are a therapeutic option, not only for malignant hematological diseases but also for benign diseases with severe multiorgan dysfunction, such as thalassemia, sickle cell disease, aplastic anemia, Fanconi anemia, or myeloproliferative syndromes (Table 1). Gene therapy has also emerged as a potential curative option but this also requires high doses of alkylating agents as part of the conditioning regimen.[6] These regimens—based on high-dose alkylating agents such as busulfan and cyclophosphamide, in combination or not with total body irradiation—are considered to carry a high risk of posttreatment permanent amenorrhea (>80%).[7] Overall, the pregnancy rate after HSCT ranges from 0.6% to 5.5%.[8] This number is slightly higher with the cyclophosphamide-based conditioning treatment used in severe medullary aplasia (12%-42%).[9] A study carried out in 70 young prepubertal girls who underwent HSCT, including those who received cyclophosphamide exclusively, showed that only 45% of them had spontaneous menarche. Up to 59% were treated with hormone replacement therapy for ovarian insufficiency as adults.[10]

Recently, new conditioning treatments have been proposed such as reduced-intensity chemotherapy (RIC) for allogeneic stem cell transplantation based on fludarabine and melphalan or treosulfan to reduce short- and long-term morbidity. However, only a few studies have evaluated the impact of these treatments on ovarian reserve. Panasiuk et al have retrospectively evaluated the impact of RIC, compared with standard treatment (busulphan/cyclophosphamide), in a population of children, including 44 girls. They showed a significant increase in spontaneous puberty rates (56.5% vs 90.5%), a decrease in hormone replacement therapy (61% vs 9.5%), and a decrease in follicle-stimulating hormone levels (64.3 vs 6.1 IU/L) using RIC compared with the conventional conditioning regimen for HSCT.[11] Although RIC is less gonadotoxic than conventional conditioning regimens, post-RIC-treatment amenorrhea was observed in 68.1% of women aged <35 years who were diagnosed with malignant or benign hematological diseases. However, around half of them had already experienced chemotherapy-induced amenorrhea before starting RIC for allogeneic stem cell transplantation.[8] Therefore, broader and longer-term studies are needed to evaluate the impact of these regimens on fertility.

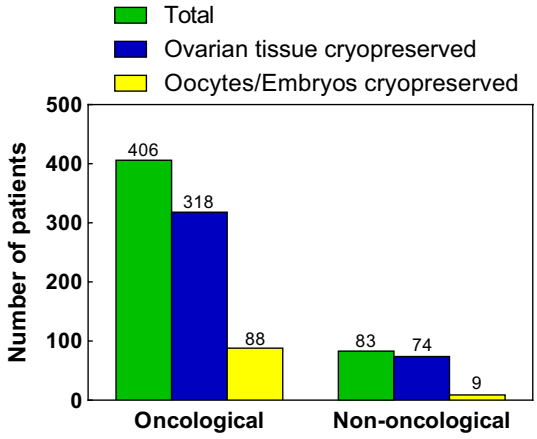


**FIGURE 1** Proportion of patients with oncological or non-oncological indications for oocytes/embryo or ovarian tissue cryopreservation in Erasme Hospital [Colour figure can be viewed at wileyonlinelibrary.com]

**Key message**

Clinicians should be aware of the infertility risks related to severe non-oncological diseases. They should provide fertility counseling and access to fertility preservation procedures before starting any gonadotoxic treatment or before any ovarian damage induced by the disease itself.

When total body irradiation is indicated,[6] additional ovarian toxicity should be evaluated according to the age of the subject and the fractioned and cumulative doses received.[12] A total dose of 2 Gy on the ovary is enough to destroy half of the follicular pool.[13] In addition to the high sensitivity of the ovary to irradiation, there is also an impact on fertility through uterine damage. A dose >14 Gy can result in uterine dysfunction with major associated obstetrical risks.[14] Uterine exposure to >25 Gy in childhood or to >45 Gy in adulthood contraindicates future pregnancy.[12]

Chronic treatments for benign hematological pathologies may also affect ovarian reserve and this should be considered when counseling women on fertility preservation. Repeated transfusions are often responsible for iron overload, leading to hemochromatosis. Iron overload induces oxidative stress, which is deleterious to organs, especially the central nervous system (dysfunction of the hypothalamic–pituitary axis) and the ovaries.[15] A study including 26 women with thalassemia (aged 29 ± 5.7 years) showed that the antral follicle count was decreased after >10 years of repeated transfusions. However, this was mainly a consequence of pituitary gland damage as the ovarian reserve, measured by antimüllerian hormone (AMH), remained broadly comparable to controls. However, AMH levels were inversely correlated with non-transferrin-bound iron and labile plasma iron levels, and were lower in women over 30 years old, suggesting that iron has a long-term gonadotoxic effect.[15] Even with iron level normalization, this process is irreversible.[16]

Finally, ovarian damage and inflammatory mediators during ischemia in vaso-occlusive crises have been proposed to be among the disrupting factors that may also explain premature ovarian aging in these women.[15]

Hydroxyurea is a standard long-term treatment administered to patients with sickle cell disease or myeloproliferative diseases. An analysis conducted on 56 young girls with sickle cell anemia, aged between 10 and 19 years, showed that 24% of them had low AMH levels (<5th centile). This group of subjects with low AMH levels was treated for a longer period compared with the group with normal AMH levels (6.8 ± 1.9 years vs 4.0 ± 2.5 years of treatment; $P = 0.007$).[17]

**TABLE 1** Major indications and specific issues in fertility preservation in non-oncological diseases

| | Pathologies | Causes and risk of POI | Fertility preservation strategies | Specific issues and limitations |
|---|---|---|---|---|
| Hematological diseases | Thalassemia<br>Sickle cell disease<br>Fanconi anemia<br>Aplastic/ myelodysplastic anemia | **Low risk:**<br>Hydroxyurea<br>Multiple blood transfusion (hemochromatosis)<br>**High risk:**<br>Conditioning for HSCT (alkylating agents/RIC/TBI) | **Low risk:**<br>Fertility counseling and follow up<br>**High risk:**<br>Oocyte cryopreservation (adolescent when feasible/ adults)<br>Ovarian tissue cryopreservation (prepubertal and pubertal patients) | Risk of thrombotic or hemorrhagic complications<br>Genetic counseling (PGD)<br>**Obstetrical risk:**<br>Pulmonary hypertension<br>Chronic renal failure<br>Alloimmunization<br>Uterine dysfunction (TBI) |
| Auto-immune diseases | SLE<br>CREST syndrome<br>Multiple sclerosis<br>Behçet disease<br>Takayasu arteritis<br>ANCA-associated vasculitis<br>Polyarteritis nodosa<br>APS-1 | **Moderate/high risk:**<br>Alkylating agents<br>Mitoxantrone<br>Autoimmune oophoritis | Oocyte cryopreservation with COS when feasible or IVM (experimental)<br>Ovarian tissue cryopreservation (prepubertal and pubertal patients or after immunosuppressive treatment started or autoimmune oophoritis)<br>GnRH agonists | Risk of thrombotic/ vascular complications<br>Risk of disease aggravation (COS)<br>**Obstetrical risk:**<br>Thrombotic and obstetrical complications (miscarriages, preeclampsia) |
| Gynecological diseases | Endometriosis<br>Ovarian cysts<br>Borderline tumors | **Low risk:**<br>Unique ovarian surgery (kystectomy)<br>Deleterious inflammatory environment (endometriosis)<br>**Moderate/high risk:**<br>Multiple surgeries | **Endometriosis/cyst:**<br>Oocyte cryopreservation<br>Ovarian tissue cryopreservation (if radical oophorectomy)<br>**Borderline tumor:**<br>A Oocyte/embryo cryopreservation after surgery with COS + letrozole | Poor ovarian response (COS)<br>Increased risk of bleeding and infection during puncture in COS |
| Genetic diseases | Fragile X<br>Turner syndrome<br>BPES<br>Galactosemia | **High risk:**<br>Accelerated ovarian senescence | Oocyte cryopreservation (postpubertal patients, if persistent ovarian function)<br>Ovarian tissue cryopreservation (for children or adolescent with spontaneous puberty, normal FSH, and AMH) | Efficacy of fertility preservation not proved<br>Genetic counseling<br>**Obstetrical risk:**<br>Potential genetic transmission<br>Maternal risks (Turner) |
| | *BRCA* carriers | **Low risk:**<br>Possible accelerated ovarian senescence<br>**High risk:**<br>Bilateral oophorectomy between 35 and 40 years | Oocytes/embryo cryopreservation | Safety of COS unknown<br>Genetic counseling (PGD) |
| | POI family history | **Moderate/high risk:**<br>Possible accelerated ovarian senescence | Oocyte/embryo cryopreservation | |
| | Hurler syndrome | **High risk:**<br>Conditioning for HSCT (alkylating agents) | Ovarian tissue cryopreservation in children | Complications due to multiple organ damage<br>Genetic counseling (PGD) |

AMH, antimüllerian hormone; ANCA, antineutrophil cytoplasmic antibody; APS-1, autoimmune polyendocrine syndrome type 1; BPES, blepharophimosis, ptosis, and epicanthus inversus syndrome; COS, controlled ovarian stimulation; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HSCT, hematopoietic stem cell transplantation; IVM, in vitro maturation; PGD, preimplantation diagnostic test; POI, premature ovarian insufficiency; RIC, reduced-intensity chemotherapy; SLE, systemic lupus erythematosus; TBI, total body irradiation.

However, no data are available in older women (>21 years old) and the long-term effects of hydroxyurea on ovarian function should be further investigated.[6] Nevertheless, this long-term treatment, associated with multiple blood transfusions, can have a deleterious cumulative effect on the ovarian reserve, and further increase the risk of ovarian failure after a conditioning regimen before a bone

marrow transplant. Although these chronic treatments generally do not require any fertility preservation procedure, appropriate fertility counseling and follow up are recommended, as well as the use of an efficient contraception method during treatment to avoid the potential teratogenicity of hydroxyurea.

A fertility preservation strategy should be considered in all young patients scheduled for HSCT. Although still experimental, ovarian tissue cryopreservation remains the most frequently offered fertility preservation strategy, as it is the only option for prepubertal girls. To obtain ovarian fragments, a laparoscopic ovarian biopsy in young women, or ovariectomy in children, is performed.[3] The ovarian cortex is processed to obtain thin slices of maximum 2-mm thickness, which are cut into small fragments before cryopreservation. The slow freezing technique is the standard procedure, although vitrification has also been recently used for ovarian tissue storage. At present, ovarian tissue transplantation remains the only clinical procedure available to restore fertility using cryopreserved ovarian tissue.[18] This is a valid option for women with benign hematological diseases. These patients are usually very young and not at risk of neoplastic cell transmission after transplantation of the cryopreserved ovarian tissue for fertility restoration.

In our center, benign hematological pathologies account for >70% of the indications for ovarian tissue cryopreservation in children. Only 2 women worldwide have undergone transplantation with cryopreserved ovarian tissue harvested at prepubertal and premenarchal ages (9 and 13 years old, respectively) to restore their fertility.[19,20] They were previously treated with HSCT for sickle cell disease[19] and thalassemia[20] and both succeeded, with 3 live births obtained after transplantation.

Oocyte cryopreservation has also been proposed in adolescents with benign hematological diseases. Oocyte cryopreservation is a well-established procedure in adults.[21] Oocytes are retrieved through transvaginal ultrasound-guided ovarian puncture after controlled ovarian hyperstimulation (COS).[22] This strategy requires around 14 days and provides around 8 mature oocytes per cycle to cryopreserve in women with cancer, varying according to the age.[22-24] Previous studies showed that vitrified oocytes have a comparable outcome to fresh ones.[1,25] According to guidelines, it is the first option for adult women facing gonadotoxic treatment.[26] As opposed to the oncological setting, there is no time constraint for COS in these indications. However, given the already heavy psychological burden for these young women,[27] with the daily need for injections and regular follow ups (transvaginal ultrasound and hormonal blood test monitoring), then transvaginal oocyte retrieval could be experienced as particularly distressing. Moreover, in 80% of these individuals, the optimal gonadotropin dosage for oocyte harvesting needs to be increased, with a higher risk of developing ovarian hyperstimulation.[22] Finally, the risk of thrombotic or hemorrhagic complications should be thoroughly evaluated before counseling these women, considering their clinical background.[28] Lavery et al reported fewer than 10 mature oocytes collected in 4 out of 8 adolescent girls with sickle cell anemia after COS, limiting the chances of future pregnancy.[22] Oocyte freezing was also proposed in a 13-year-old with premenarchal myelodysplastic syndrome. Twenty oocytes were collected, including 8 in metaphase II. The 12 remaining immature oocytes were matured in vitro. Ten reached metaphase II after 24 h and were vitrified.[29] However, the potential for embryonic development from these oocytes is still unknown. Although feasible, oocyte freezing appears to be a suboptimal option for fertility preservation in adolescents with benign hematological diseases compared with ovarian tissue cryopreservation.

Finally, fertility counseling should include the consideration of obstetrical risks that may develop from the chronic complications of sickle cell anemia. These complications, such as pulmonary hypertension, may contraindicate pregnancy.[30,31] In these cases, women can be advised to use a surrogate where the law permits. Chronic renal failure and red blood cell alloimmunization can be other challenging complications that should be managed by an experienced multidisciplinary team.[32,33]

## 3 | AUTOIMMUNE DISEASES

In our center, autoimmune diseases account for 41% of non-oncological indications for ovarian tissue cryopreservation in adults and 15% in children. In the majority of cases, these women require an immunosuppressive treatment with alkylating agents in an acute phase of the disease, with severe organ damage (Table 1). Cyclophosphamide is the standard treatment in pediatric populations for systemic lupus erythematosus (SLE), granulomatosis, or other severe forms of vasculitis.[34] The risk of POI after treatment depends on the patient's age and on the cumulative drug dose, but exceeds 60% in women older than 30 years.[35] To reduce this risk, cyclophosphamide can be partially replaced by less gonadotoxic agents, such as mycophenolate mofetil, rituximab, or calcineurin inhibitors, when feasible.[36,37] Autoimmune polyendocrine syndromes (eg antiphospholipid syndrome) associated with a mutation of the *AIRE* gene, lead to severe immune damage in several endocrine organs, including the ovaries. Multiorgan and vascular involvement at childbearing age need specific and personalized care, including ovarian function monitoring and counseling on fertility preservation, contraception, and obstetrical issues (Table 1). These women are particularly at risk of thrombotic and obstetrical complications, such as recurrent miscarriages or preeclampsia.[38] Women treated with cyclophosphamide should be informed of the subsequent infertility risk, as >80% of them wish to preserve their fertility.[36] In adults, the first established option is oocyte/embryo cryopreservation.[5] However, estradiol elevations induced by COS could aggravate SLE. Although rare, severe complications have been reported in women with SLE during COS such as pulmonary embolism and arterial and venous thromboses.[39] These complications are generally associated with ovarian hyperstimulation syndrome. COS can be coupled with a prophylactic therapy (anticoagulant and corticosteroid) but general recommendations restrict the use of COS to patients who are in a latent phase of the disease, without any pulmonary or cardiac manifestation or without

a history of deep vein thrombosis.[39] As cyclophosphamide is generally indicated in the acute phase of SLE, management of fertility preservation is particularly complex in these women.

Mitoxantrone is a second-line drug in individuals with multiple sclerosis who have worsening relapse or progressive disease, and who do not respond to interferon-β or glatiramer acetate. A recent prospective study conducted on 371 women with multiple sclerosis found a transient amenorrhea rate of 27% and a persistent amenorrhea rate of 17.3%.[40] No participant <25 years of age developed persistent amenorrhea.[40]

Only a few cases of oocyte cryopreservation have been described in the literature in women with autoimmune vasculitis.[36,41] Severe complications were reported in a 25-year-old woman with an acute phase of mixed connective tissue disease. After an oocyte cryopreservation procedure for fertility preservation, she presented with a cascade of multiorgan system dysfunctions probably exacerbated by increased estradiol levels and the sedation required for oocyte retrieval.[42] Hence, the risk of multiorgan complications can be life-threatening in patients in the acute phase of the disease. To avoid these risks, some authors have suggested collecting immature oocytes during a natural menstrual cycle, followed by in vitro maturation and vitrification.[43] However, the efficacy and the safety of this procedure in women who have autoimmune diseases have yet to be demonstrated. Hence, ovarian tissue cryopreservation represents an interesting alternative in young women, in the absence of surgical contraindications.[12] This technique can also be performed after the initiation of chemotherapy if previous health conditions did not allow for the safe performance of laparoscopic surgery under general anesthesia before the start of the treatment. Indeed, anesthesia can also carry major risks for these women. A 26-year-old patient diagnosed with SLE developed acute respiratory distress syndrome due to a buccal and nasal hemorrhage after extubation during an ovarian tissue cryopreservation procedure and died 7 days later from sepsis.[3]

A multidisciplinary and cautious risk assessment is crucial before offering any invasive procedure for fertility preservation in patients with acute autoimmune disease. These procedures are usually not recommended during the acute phase of the disease when severe vascular and/or organic lesions are present (eg glomerulonephritis, pulmonary hypertension, ischemia). When cryopreservation of oocytes or ovarian tissue is not feasible, ovarian pharmacological protection with the use of gonadotropin-releasing hormone agonists can be proposed as an experimental noninvasive option during cyclophosphamide treatment.[12,34,36] In some cases, this may even reduce the risk of atherosclerosis (in SLE) or encephalomyelitis (in multiple sclerosis).[35,44] Based on large randomized prospective trials, this controversial approach has produced positive results in preventing adjuvant and neoadjuvant treatment-induced amenorrhea in women with breast cancer.[45] Several observational or retrospective studies have analyzed the effectiveness of these treatments in autoimmune diseases.[46,47] Although the number of individuals analyzed was low, the data suggested a beneficial effect of this treatment on ovarian reserve and POI rate.

Finally, ovarian reserve depletion can also be induced by the disease itself. A study carried out in 33 women with SLE who never received cyclophosphamide showed a decrease in their ovarian reserve compared with matched controls.[48]

Autoimmune oophoritis associated with autoimmune polyglandular syndrome type 1 or 2 is responsible for 2%-10% of POI cases[49] related to the presence of circulating steroid-cell autoantibodies directed against steroidogenic enzymes, such as 21-hydroxylase, 17-hydroxylase, and cytochrome P450 side-chain cleavage, or adrenal enzymes (eg adrenal cortex antibodies).[49] Recent studies have shown that ovarian degeneration is the result of the destruction of growing theca cells. As a consequence, there is a lack of substrate for estradiol synthesis and a subsequent elevation of circulating gonadotropins. Unlike idiopathic POI, inhibin B may be elevated in these women, demonstrating the presence of functional granulosa cells and probably intact quiescent follicles.[50] In young women diagnosed with an autoimmune POI and high inhibin B levels, preservation of fertility should be considered before the ovarian reserve is completely destroyed.[49] In this case, ovarian tissue cryopreservation remains the option of choice, but the likelihood of completion of folliculogenesis after tissue grafting to restore fertility remains uncertain. In vitro follicular growth could be a future option but it is still experimental.[51]

## 4 | GYNECOLOGICAL PATHOLOGIES

Gynecological conditions represent >40% of non-oncological fertility preservation indications in adults in our center, including endometriosis, recurrent ovarian cysts, and ovarian borderline tumors. Depletion of the ovarian reserve is usually the result of repeated ovarian surgery. Indeed, cysts recur after surgery in 30%-50% of cases for endometrioma and in 4%-10% of cases for dermoid, serous, or mucinous cysts.[52] Endometrioma surgery seems to be more deleterious to the ovarian reserve than surgery for the other types of benign cysts.[53] Moreover, endometriosis has a direct negative effect on the ovarian reserve, as shown by the lower AMH levels and antral follicle count reductions observed in these women.[54] This might be explained by ovarian fibrosis, observed in 55% of the ovaries with endometriomas, and by the toxic effects of oxidative stress on ovarian follicles.[55] Considering these effects on ovarian reserve and the high risk of recurrence, fertility preservation options should be discussed in young women with these conditions. Moreover, additional action should be proposed, such as oral contraceptives, to reduce the risk of recurrence of endometriosis.[56] The benefits of fertility preservation should be carefully evaluated according to the severity of the disease (bilateral or unilateral), the type of surgery previously performed, recurrence, and ovarian or peritoneal involvement.[57,58] As emergency fertility preservation is not mandatory, the first option is oocyte/embryo vitrification after COS. However, the efficiency of the procedure is reduced in women who underwent previous endometrial surgery. Several cycles may be required to obtain enough oocytes and ovarian puncture might be difficult due

to pelvic anatomy distortions. On the other hand, the risk of infection (0%-1.7%) must be considered when retrieving oocytes in cases of severe endometriosis.[53] In a recent study of 24 young women with benign ovarian cysts, 38% had a poor response to COS with <4 oocytes collected. The median number of vitrified oocytes per patient was only 4.4 ± 4.[52] Cryopreservation of ovarian tissue can be offered only in cases of mandatory radical oophorectomy, as this might aggravate the risk of POI if additional healthy ovarian cortex is removed from the remaining ovary.

One-third of women with borderline ovarian tumors are under 40 years old and >80% are diagnosed at stage I, for which treatment is curative in >90% of cases.[59] Fertility-sparing approaches should always be proposed in young women of childbearing age, especially in the case of a serous tumor. However, this type of tumor is frequently bilateral (30%) and the risk of recurrence after conservative surgery is about 20%-30%.[60] Considering the recurrence risk, the possibility of fertility preservation must be discussed.[61] Although deleterious hormonal effects on the tumor have not been clearly demonstrated, COS before surgery is not recommended. Data on the feasibility and safety of performing oocyte or embryo cryopreservation after surgery are limited but reassuring, with a recurrence rate similar to controls.[60] However, administration of an aromatase inhibitor (letrozole) is recommended during COS in order to limit the potential deleterious impact of supraphysiological estrogen levels.[61] Ovarian tissue cryopreservation has also been offered in this context and can be performed during tumor resection. However, the risk of ovarian involvement or recurrence remains high, even when the contralateral ovarian cortex is cryopreserved; the use of this tissue for future transplantation is questioned.[62] Therefore, oocyte and embryo vitrification are currently the best options. In the case of unilateral ovariectomy, immature oocytes can also be identified ex vivo and subjected to in vitro maturation and vitrification.

## 5 | GENETIC DISORDERS

Chromosomal abnormalities are found in 10%-12% of POI cases and primarily involve the X chromosome.[63] As a diagnosis of POI is often made as a result of primary or secondary amenorrhea, it is usually too late for fertility preservation procedures. Etiology might be suggested by a specific phenotype, such as Turner's syndrome or blepharophimosis–ptosis–epicanthus inversus syndrome type 1, present before occurrence of POI. Some cases will be diagnosed before birth, such as Turner syndrome suspected at the first-trimester ultrasound and diagnosed by chorionic villus sampling or amniocentesis, or after birth, such as galactosemia found during neonatal screening.

Although recommendations limit screening to karyotype and *FMR1* mutation testing when genetic etiologies are suspected,[63] several autosomal gene mutations such as *BMP15*, *GDF9*, *FOXL2*, and *FSHR* have also been implicated as potential causes of POI and can be sequenced within a gene panel to expand diagnostic tests. Gene panels of candidate genes involved in oocyte-specific transcription factors, folliculogenesis, and ovarian steroidogenesis are being explored in experimental settings.[64] The genomic diagnostic approach has expanded with the identification of copy number variations through comparative genomic hybridization arrays and with complete genome sequencing in family cases. The pathophysiological background has still to be fully explored.[64] These new opportunities will allow clinicians to target women at risk due to their family history. Ovarian reserve depletion can be anticipated and, according to age and risk of early POI, fertility preservation can be offered.[65] In cases of early diagnosis of a genetic predisposition to POI, ovarian tissue[66] or oocyte[67] freezing can be proposed according to the age at diagnosis. In women with Turner syndrome with persistent ovarian function, oocyte cryopreservation can be offered as the first option.[68] During childhood, the cryopreservation of ovarian tissue remains the only available option. In a large series of 57 girls with Turner syndrome up to the age of 20 years, follicles were found in the ovarian cortex in 26%.[69] Between 12 and 16 years of age, spontaneous puberty, and normal follicle-stimulating hormone and AMH were considered to be positive predictive factors for the presence of follicles within the ovarian cortex, whereas a 45X karyotype had a negative impact.[69] At present, the efficiency of these procedures in genetic indications to restore fertility has not been proven. Moreover, fertility preservation raises several issues in this context. Women with Turner syndrome should be counseled regarding potential maternal risks during pregnancy, according to the presence of renal or cardiac malformations. Moreover, oocyte competence might be reduced by the genetic disorder itself. Finally, the risk of genetic disorder transmission to the progeny also raises ethical questions.

Women with a family history of POI without an identified genetic disorder might also be at risk of developing POI. In this situation, fertility preservation counseling is challenging. Nevertheless, the British Menopause Society recently stated that women with a strong family history of POI should be advised to undergo oocyte cryopreservation.[70]

Other genetic disorders, such as *BRCA* mutations, do not directly induce POI but might affect reproductive potential due to the high risk of developing ovarian and breast cancer. The American College of Obstetricians and Gynecologists recommends performing bilateral oophorectomy between 35 and 40 years of age or when childbearing is complete in all *BRCA1* mutation carriers, whereas *BRCA2* mutation carriers can postpone this for 5 years.[71] Therefore, there is an indication for oocyte/embryo cryopreservation when pregnancy is postponed.[1] Moreover, as 30% of women wish to perform a preimplantation genetic diagnosis to select healthy embryos before transfer, oocyte retrieval will be mandatory for this technique and could be offered at a young age before childbearing is desired.[72] Finally, the genetic disorder itself might impact reproductive potential[73] and the performance of fertility preservation.[74]

Finally, rare genetic disorders such as Hurler syndrome (mucopolysaccharidosis type 1) might need a conditioning treatment for HSCT. In those cases, ovarian tissue cryopreservation can also be proposed.[66]

## 6 | CONCLUSION

Fertility management in women affected by benign conditions is less often a primary concern than it is in oncological patients. The reason for this is that the medical team often has a lack of information. Currently, all fertility preservation efforts are concentrated in oncology centers. However, many women affected by benign conditions may derive benefit from preserving their fertility. In these conditions, the pathology itself and/or the treatment can have a negative impact on their ovarian reserve. However, each fertility preservation indication must be considered with care, in a multidisciplinary setting, especially for autoimmune diseases, to avoid any risk of severe complications. Moreover, long-term studies are needed to better understand the long-term effects of novel treatments on fertility in non-oncological settings.

## CONFLICT OF INTEREST

The authors have stated that there are no conflicts of interest.

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