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FERTILITY PRESERVATION

Fertility considerations in young women with hematological malignancies

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Abstract The need for practice guidelines for fertility preservation in young women with hematological malignancies has been increased. To develop recommendations, publications relevant to fertility preservation and hematological cancers were identified through a PubMed database search and reviewed systematically, focusing on the effects of oncological treatments on fertility as well as on the efficacy, feasibility and risks of existing fertility preservation methods.

Keywords Hematological malignancy · Fertility · Fertility preservation · Chemotherapy · Lymphoma · Leukemia, cancer

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Introduction

With the development of combination chemotherapy for the treatment of hematological malignancies, prognoses have dramatically improved, shifting areas of focus towards preventing post-treatment complications, such as infertility. At the same time, the last decade has seen significant progress in the field of fertility preservation. Several methods are now available, and it is our ethical and moral responsibility to discuss these issues with all children and women with reproductive potential, who are subjected to potentially gonadotoxic therapy.

Counseling on different fertility preservation methods

Several options have been proposed for the preservation of fertility in cancer patients. The choice of the most suitable strategy depends on different parameters, such as age, type of gonadotoxic treatment, timing of chemotherapy, partner status and risks related to the technique. Fertility counseling should be adapted to individual patients and based on comprehensive knowledge on the efficacy, risks and technical aspects associated with the different fertility preservation methods.

> The most important issue to consider is ensuring that the intervention does not harm the patient or alter her prognosis by delaying cancer treatment.

Hormone therapy

On the basis of observations that premenarchal girls are less affected by gonadotoxic treatments, oral contraceptives and GnRH agonists have been used to create a hypogonadotropic state, with low FSH and LH concentrations causing decreased follicular recruitment. However, no protective effect of oral contraceptives has been identified [1–3], while

doubts remain about the efficacy of GnRH agonists. Initial studies showing a protective effect were non-randomized, with small patient numbers and historical controls, and used menstruation, not fertility, as an end-point measure. Meta-analyses [4–7] and three randomized controlled trials (RCTs) showed a protective effect of GnRH agonists [8–10]. However, another RCT in women with Hodgkin's lymphoma treated with highly gonadotoxic regimens was prematurely halted due to lack of protection [11] and the recent ZORO study reported no significant difference in the restoration of spontaneous cycles and hormone profiles after GnRHa co-treatment compared with controls in patients up to 45 years of age treated for breast cancer [12]. As far as protective mechanisms are concerned, there is no clear evidence that initiation and early stages of follicle growth are gonadotropin-independent. Although other mechanisms may be involved, the decreased toxicity observed in prepubertal girls is more likely to be related to follicular density and other anatomical factors [13] than to the absence of LHRH secretion. Moreover, treatment with GnRH agonists for over 6 months leads to loss of bone mass [14] and there is a theoretical risk of reducing the efficacy of chemotherapy when using GnRH agonists in patients with estrogen receptor-positive breast cancer. At present, the main advantage of hormone treatment might be prevention of uterine bleeding, especially in women with hematological malignancies. More RCTs need to be undertaken before any definitive conclusions can be reached.

Embryo cryopreservation

IVF and cryopreservation of embryos is a well established procedure for fertility preservation. Several issues should nevertheless be discussed when considering this technique for fertility preservation purposes.

- Although donor sperm can be used to obtain embryos, this technique is mostly reserved for adult women with a partner. However, living with cancer, enduring oncological treatment and being a cancer survivor are psychologically very demanding. Even when a relationship appears secure, it is impossible to guarantee that this will remain the case. Other techniques that preserve the patient's own fertility should therefore be proposed in addition to embryo cyropreservation.
- The latest findings from the Society for Assisted Reproductive Technology and the European IVF Monitoring Program report a pregnancy rate of 34 % following frozen-thawed embryo transfer in women under 35 years of age and an overall pregnancy rate of 19 % [15, 16]. However, there are no published data on pregnancy rates after IVF carried out as an emergency procedure in cancer patients. The mean number of oocytes retrieved and embryos obtained in women undergoing IVF before chemotherapy is not different from women undergoing routine IVF [17–19], although the duration of stimulation and gonadotropin doses may be increased [20]. An average of 10 oocytes [21] and 6 embryos [19] (60 % fertilization rates) [22, 23] may be expected, but this is variable and dependent on the woman's ovarian reserve and age.
- A classic IVF cycle starts during the early follicular phase and takes approximately 2–5 weeks. This delay before cancer treatment could potentially alter the prognosis, so it is essential to have the oncologist's approval before discussing this option with the patient. However, luteal phase IVF is now feasible, reducing the delay before chemotherapy and yielding similar results to follicular phase IVF [24].
- Emergency IVF is not recommended after 1–2 courses of chemotherapy. Indeed, the number of embryos obtained is very low [25] and concerns have been raised about the quality of embryos derived from oocytes harvested after recent exposure to chemotherapy and the risks of increased congenital malformations [26].
- In some cancers (breast cancer), elevated estrogen levels associated with ovarian stimulation and IVF may adversely affect the tumour growth [21]. Stimulation protocols using aromatase inhibitors in combination with exogenous FSH appear to be preferable in women suffering from such malignancies [27].
- Protocols using GnRH antagonists should be favoured, as they are associated with a lower risk of ovarian hyperstimulation syndrome (OHSS) [23].
- The risk of OHSS can further be decreased by triggering final oocyte maturation by GnRH agonists [28].
- As far as the actual cryopreservation technique is concerned, there is no statistical difference between pregnancy rates after slow freezing or vitrification of embryos [29]. The method of choice should be determined by the fertility centers based on their own experiences and success rates.

Alternatively, in vitro maturation (IVM) of immature oocytes followed by fertilization and cryopreservation can be considered.

- IVM has become an effective treatment option for many infertile women, resulting in the birth of over 2000 healthy infants without any increase in fetal abnormalities or miscarriage rates in comparable subjects [16].
- HCG is administered when the largest follicle seen on ultrasound measures 12 mm, and oocytes are collected approximately 36 h after HCG injection [30] Compared to the 2–5 weeks required for a stimulated IVF cycle, immature oocyte retrieval can be done within 2–10 days. Immature oocytes can even be collected during the luteal phase with similar results to follicular phase retrieval [16, 31].

- In experienced centers, women undergoing IVM before cancer treatment can expect retrieval of 8–17 immature oocytes, maturation rates of 50–60 % and fertilization rates of 60–70 % [30, 31].
- The rapidity of the technique, prevention of elevated estrogen levels, elimination of the risk of OHSS, and possibility of application to oocytes obtained during ovarian tissue sampling for cryopreservation [32, 33] make this technique attractive for fertility preservation in young women with cancer.
- However, overall pregnancy rates remain lower than those achieved by regular IVF cycles [34].

Oocyte cryopreservation

Cryopreservation of oocytes obtained by IVF or IVM represents an alternative method for fertility preservation, especially in women without a partner. The first birth after human oocyte cryopreservation was reported back in 1986 [35]. Low oocyte survival rates and low fertility potential due to problematic freezing processes were impediments to successful reproduction, with live birth rates of just 2 % per oocyte [36]. Vitrification protocols have since greatly improved upon these results.

In experienced hands, vitrified oocytes obtained after IVF in a non-oncological population yield 80–95 % survival rates after thawing, 75 % fertilization rates, clinical pregnancy rates per cycle of 45–65 % and live birth rates of 40 % [16, 37]. Pregnancy rates in centers specialized in egg donation programs are similar with fresh and vitrified oocytes [38].

The first live birth achieved after vitrification of mature oocytes before cancer treatment was reported in 2007 [39]. Live birth rates of 20 % per cycle have been documented after vitrification of in vitro-matured oocytes [40]. However, to our knowledge, no pregnancies have been reported after fertilization of in vitro-matured oocytes harvested and vitrified before cancer therapy.

Concerns were raised about the toxicity of high concentrations of cryoprotectants needed for vitrification of oocytes, but no increase in congenital anomalies was observed in a series of more than 1000 infants born following oocyte vitrification [40, 41].

Success rates of vitrification of mature and in vitro-matured oocytes in the context of cancer are less widely documented. As previously mentioned, the number of oocytes retrieved for IVF or IVM in women with cancer does not appear to be different from non-oncological populations. However, very little has been published on pregnancy rates, making it difficult to give any clear idea of likely success rates when discussing this alternative with women prior to cancer treatment.

Ovarian tissue cryopreservation and transplantation

Harvesting and cryopreservation of ovarian tissue before sterilizing chemo- and/or radiotherapy has been increasingly implemented and documented during the past decade. The main aim of this strategy is to reimplant ovarian tissue in case of premature ovarian failure (POF), and its major advantage is that it is applicable in prepubertal girls [42] and women who cannot delay the start of chemotherapy. The first live birth obtained using this technique was published in 2004 [43].

At least 13 pregnancies have since been described after reimplantation of frozen-thawed ovarian tissue [44], with estimated pregnancy rates of 30 % [23]. An analysis of the literature yields a wealth of information that can be used when counselling such patients.

Ovarian tissue cryopreservation

- Ovarian tissue harvesting can be performed by laparoscopy at any age, without postponing chemotherapy.
- A maximum age limit of 37 years is recommended. However, decisions should be individualized based on ovarian reserve tests such as antral follicle count and AMH levels. All pregnancies but one achieved by this technique were in women who had had their ovarian tissue cryopreserved before the age of 30.
- The risks of general anesthesia should be assessed, particularly in patients with mediastinal masses.
- The quantity of ovarian tissue removed should be influenced by the expected probability of POF.
- At the time of ovarian sampling, visible follicles can be aspirated and IVM performed [32, 33].
- Biopsies should be histologically evaluated to exclude cancer cells and confirm the presence of follicles.
- If necessary, transport is feasible over an extended period of time (up to 20 h) [45].
- The most efficient method of cryopreservation at present appears to be slow freezing.

Ovarian tissue reimplantation

- The oncologist's approval should be obtained before proceeding with ovarian tissue reimplantation.
- All pregnancies achieved after reimplantation of frozen-thawed ovarian tissue occurred after orthotopic reimplantation.
- Orthotopic ovarian tissue reimplantation can be performed by laparoscopy or laparotomy, and the choice of technique depends on the individual surgeon's skill and experience.
- In the largest reported series [44], the peritoneal window created close to the ovarian hilus and the ovarian medulla both appear to be equally efficient sites of

reimplantation. The disadvantage of the peritoneal window is that it requires two surgical procedures.
- Large strips (8–10 mm × 5 mm) and small cubes (2 × 2 mm) of tissue both restore ovarian function.
- Restoration of ovarian function occurs 3½–6½ months after reimplantation, and takes longer in patients who underwent chemotherapy before cryopreservation than in those who did not.
- Persistence of restored ovarian function has been described for up to 7 years. This duration is shorter in women who received chemotherapy before cryopreservation, and longer in patients younger at the time of cryopreservation.
- Several women have obtained more than one pregnancy after ovarian tissue reimplantation.
- More than 50 % of women who achieved pregnancy were able to conceive naturally.
- In women undergoing IVF, an increased rate of empty follicle syndrome (as high as 29–35 %) was observed [45–47].
- No congenital anomalies have so far been encountered in children born using this technique.
- A significant concern is the possibility of ovarian tissue harboring malignant cells. Therefore, all available tests to exclude minimal residual disease should be performed. Besides histological evaluation, analyses by PCR and xenografting to nude mice are available options. In the case of risk of contamination, ovarian reimplantation should be avoided. Advances in research in the field of IVM or reimplantation of isolated follicles may offer hope to these women in the future [48–54].

Ovarian transposition

When radiotherapy is indicated, ovarian transposition can be proposed in order to displace the ovaries away from the radiation field. In case of craniospinal irradiation, the ovary can be fixed laterally as far as possible from the spine. In case of pelvic irradiation, the ovary could be moved outside the pelvis, which may require section of the utero-ovarian ligament and fallopian tube. The ovary is anchored, as high as possible, to the anterior abdominal wall, laterally in the paracolic gutter. Titanium clips are placed on the two opposite borders of the ovary to allow radiological identification prior to radiotherapy. The success of ovarian function preservation by means of ovarian transposition prior to radiotherapy ranges from 16 % to 90 % [55–58].

Success rates are affected by the degree of scatter radiation, vascular compromise, patient age, radiation dose, and use (or not) of concomitant chemotherapy [59]. When the ovaries are transposed to an abdominal position, spontaneous pregnancy may not be possible unless a second procedure is performed to relocate the ovaries back to the pelvis. Furthermore, should these patients need IVF in the future, oocyte retrieval may be technically more challenging. Candidates for ovarian transposition should therefore be selected carefully, taking into account all variables that may affect its success rate. Ovarian cryopreservation can be performed at the same time of transposition.

Specific counseling in case of hematological malignancies

Due to the demographics of hematological malignancies, especially acute lymphoblastic leukemia and Hodgkin's lymphoma, a large proportion of patients will be candidates for fertility preservation. Moreover, hematopoietic stem cell transplantation (HSCT) has a prominent role in cancer treatment and is preceded by highly gonadotoxic chemo- and/or radiotherapy resulting in high ovarian failure rates (70–100 %).

Each hematological malignancy has a unique set of fertility considerations relating to the disease itself, the gonadotoxic potential of treatment protocols, and the age of patients.

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is characterized by peak incidence between 20 and 29 years of age (4.4/100 000) and overall 5-year survival rates of 87 % and even 96 % in women under 20 years of age [60].

There are several chemotherapeutic regimens for HL that include ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and regimens containing alkylating agents (MOPP, CHOP, BEACOPP).

Treatment protocols like ABVD, devoid of alkylating agents, pose little or no documented risk of POF [61–64]. On the contrary, protocols containing alkylating agents, especially procarbazine and cyclophosphamide in cumulative doses, are associated with an increased (up to 70 %) risk of POF [11]. Age is an independent risk factor for POF in HL [63]. The younger the patient, the lower the risk of POF. However, damage to the ovarian reserve may only become apparent years later in women still at reproductive age.

Current guidelines for the treatment of HL [64, 65] take into account the different effects on fertility of the various regimens. ABVD protocols associated with involved field irradiation are considered standard treatment for limited disease stages. Protocols containing alkylating agents are recommended for advanced stages, refractory disease and relapse. In some cases, HSCT may be required, associated with highly gonadotoxic conditioning regimens.

As refractory disease and relapse cannot be predicted, fertility issues and preservation methods should be discussed with all patients under the age of 37. If chemotherapy can be postponed, embryo or oocyte cryopreservation should

be considered. Unlike in male HL, there is no evidence of pre-treatment fertility impairment [22]

Cryopreservation and reimplantation of ovarian cortex have proved effective in women with HL. Indeed, at least 4 women who conceived as a result of this technique had previously suffered HL [44]. None of them experienced disease recurrence after ovarian tissue reimplantation. Several studies have suggested that ovarian tissue transplantation may be considered safe in case of HL [66–68], but one case report [69] showed ovarian involvement in stage III HL. The ovaries were also found to be affected by HL in 1–5 % of autopsies [70, 71]. In some HL cases, large mediastinal masses may increase anesthetic risks and ovarian tissue harvesting may therefore be contraindicated.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma (NHL) is less common than HL in women under 30 years of age (0.6 to 3.3/100 000) and is associated with 5-year survival rates of 69 % overall and 84 % in women under 20 years of age [60]. Different forms of NHL exist, as well as different treatment modalities, including local radiation, chemotherapy, immunotherapy and HSCT. Most treatment regimens include alkylating agents. There are far fewer data available on fertility after treatment for NHL than HL, though female survivors of childhood NHL appear to be at low risk of POF [72]. Limited studies in adults also report low percentages of gonadal dysfunction [73–75].

Planned treatment protocols and a safe delay before the start of therapy should be discussed with hematologists before considering fertility preservation options. Animal studies have demonstrated a risk of transmission of NHL by ovarian transplantation [76]. Caution should therefore be exercised and all available methods applied to exclude the presence of lymphoma from ovarian biopsies before considering ovarian transplantation.

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Indeed, 75 % of ALL cases occur in children. Five-year ALL survival rates are 66.4 % overall and 90 % in children under 15 years of age [60].

The rate of treatment-induced infertility in leukemia patients depends on whether HSCT, with its highly gonadotoxic conditioning regimens, is undertaken [77]. Contemporary treatment protocols for ALL use lower doses of gonadotoxic agents, particularly cyclophosphamide, and are thus unlikely to cause infertility [78–80]. Thus, fertility preservation options should be reserved mainly for patients undergoing HSCT. As most ALL cases occur in children, ovarian tissue cryopreservation is the best option to preserve fertility, possibly associated with oocyte aspiration at the time of ovarian harvesting, in vitro maturation and cryopreservation by vitrification. However, ovarian reimplantation carries a high risk of reintroducing leukemic cells. Indeed, PCR methods and xenografting to nude mice using ovarian biopsies from women with ALL showed leukemia cells in 70 % of cases [81]. Not all cases of ALL display genetic markers and, so far, there are no sensitive molecular methods to evaluate the risk of contamination by malignant cells. Women suffering from ALL or parents of girls with the disease should be clearly informed that any harvested tissue will only be able to be used in the future for IVM or reimplantation of isolated follicles. Postponing cryopreservation until after induction chemotherapy might be an option to eradicate leukemic cells from biopsies, but one cycle of chemotherapy is not sufficient to purge the ovary of malignant cells [81, 82] while it may already be deleterious to oocyte quality [25, 83]

In older women with leukemia, oocyte or embryo cryopreservation may be impossible, as treatment should usually not be delayed for more than 1 week.

Acute myeloid leukemia

Acute myeloid leukemia (AML) has 5-year survival rates of 24 % overall and 60 % in children under 15 years of age [60]. In AML, regimens devoid of alkylating agents are most commonly used and thus infertility may be even less common than in ALL [84]. Although less extensively documented, fertility preservation issues in AML are probably comparable to those in women with ALL.

Chronic myeloid leukemia

Nowadays, chronic myeloid leukemia (CML) is treated with inhibitors of tyrosine kinase, such as imatinib (Gleevec). HSCT is used in case of failure of drug treatment. Imatinib is not thought to impair fertility in women [22]. To date, there is insufficient data on the effects of second-generation tyrosine kinase inhibitors on reproductive function, although successful pregnancies have been reported after use of these drugs [85, 86]. Fertility preservation methods should be applied in case of HSCT. As in acute leukemia cases, ovarian tissue may be infiltrated by the disease [81, 82, 87]. As the presence of the BCR-ABL gene is characteristic of the disease, molecular detection of leukemic cells in ovarian tissue can always be carried out. It is important to note that patients who show a positive response to imatinib are advised not to interrupt their therapy, because of the risk of relapse and progression. Moreover, patients with CML, especially those treated with total body irradiation (TBI) followed by allogeneic bone marrow transplantation (BMT), may be at unique risk of relapse with subsequent

pregnancy [88]. Indeed, the immunological surveillance required to sustain remission after BMT might be compromised by the immunotolerant state of pregnancy, contributing to this increased risk of relapse. A patient on Gleevec should only try to conceive if the oncologist allows her to stop the medication during pregnancy. Very close monitoring by oncologists, as well as obstetricians, should however be recommended. Although the experience is limited, several successful pregnancies and deliveries have been reported in patients on Gleevec.

Hematopoietic stem cell transplantation

The rate of post-HSCT infertility is greatly influenced by the gonadotoxic potential of the conditioning regimen and the age of the patient at the time of transplantation [13]. Myeloablative pre-transplant conditioning regimens are based on TBI and/or alkylating agents. Most patients treated with TBI experience early gonadal failure and the reported incidence of pregnancy is less than 3 % [88, 89, 91].

Myeloablative therapy using cyclophosphamide, busulfan or melphalan has been suggested as an alternative approach to avoid the side effects of irradiation [78, 91, 92]. Younger age at the time of HSCT reduces the risk of immediate ovarian failure, but fertility will nevertheless be impaired over time.

The type of transplant (allogeneic versus autologous) or previous treatment with alkylating agents have not yet been shown to affect the prevalence of POF [93].

Overall pregnancy rates after HSCT remain low, ranging from 0.6 to 11 % depending on study [13, 88, 90, 94]. Pregnancies in women subjected to HSCT are likely to have successful outcomes in over 80 % of cases, and there is no evidence of increased congenital abnormalities [88, 94]. However, women undergoing TBI have higher rates of preterm deliveries, cesarean sections and low birth weight babies [88, 90] especially if TBI was performed during childhood [22].

Because of the high risk of POF, it is mandatory to discuss fertility preservation options with women and girls requiring HSCT. Cryopreservation of embryos, oocytes and ovarian tissue can be proposed in this instance.

Conclusions

It is difficult to precisely assess the risk of infertility after oncological treatment in children and young women with hematological malignancies, because disease evolution is never completely predictable. Patients initially at low risk of gonadal failure may eventually require more aggressive treatments [42]. Immediate POF is less likely in young patients, but the risk remains. Fertility counselling should be given to all women with reproductive potential and children and their parents, subjected to potentially gonadotoxic treatment, All available methods should be discussed during consultation. Primary care physicians and oncologists should be aware of the available fertility preservation options to expedite referrals to fertility specialists.

In addition, social, legal and ethical issues should be taken into account. The two most important issues are ensuring that the intervention does not harm the patient by dangerously postponing cancer treatment and that no remnant cancer cells are reintroduced by subsequent transplantation, especially in hematological malignancies. IVM followed by cryopreservation of oocytes or embryos can be an alternative method in adults. Finally, it is imperative to provide the patient clear information on the expected results and risks of the procedures.

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