Management of fertility in patients treated for Hodgkin lymphoma

by Stephanie Harel, Christophe Ferme, and Catherine Poirot

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Management of fertility in patients treated for Hodgkin lymphoma

Running title: Management of fertility for Hodgkin lymphoma

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Key words: Hodgkin lymphoma, gonadal toxicity, fertility preservation, female, male

Abstract
The risk of developing premature ovarian failure and azoospermaia is a major concern in long-term survivors treated for Hodgkin lymphoma. Alkylating chemotherapy containing procarbazine and/or cyclophosphamide, causes prolonged azoospermaia in 90-100% of men and premature ovarian failure in 5-25% of women under the age of 30. The risk of infertility increases with the cumulative dose of alkylating agents and the risk is high after salvage therapy including conditioning and autologous or allogeneic transplantation. The doxorubicin, bleomycin, vinblastine, dacarbazine regimen is associated with a lower risk of gonadal damage; the rate of infertility is less than 10%. The risk of premature ovarian failure is limited after the doxorubicin, bleomycin, vinblastine, dacarbazine regimen, however age is an important factor, women over 30 years of age are at a much higher risk of ovarian failure. Semen cryopreservation should be offered routinely, especially before initial treatment with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone or salvage therapy with high-dose chemotherapy and autologous transplantation. For women with a stable partner, in vitro fertilization for embryo cryopreservation is a routine procedure but can be offered to only a small number of patients and requires a delay in treatment initiation for at least 4 weeks. Cryopreservation of mature or immature oocytes remains experimental. Ovarian tissue cryopreservation is promising but has so far resulted in only a small number of pregnancies and births. This method usually involving the removal of an entire ovary, is only proposed before treatment leading to a high risk of infertility. Analoguees of LHRH were investigated in order to preserve fertility in women, but are not recommended in the absence of studies demonstrating their effectiveness. The risk of secondary infertility should be discussed with patients from the time of the diagnosis and requires multidisciplinary collaboration between haematologists and Assisted Reproductive Techniques (ART) teams.

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**Introduction**
The treatments currently administered can cure about 80% of patients with Hodgkin lymphoma, all stages combined, but progress is still required in order to reduce the potential side effects of treatment and particularly long-term adverse effects. The evolution of treatment has resulted in the maintenance of chemotherapy and radiotherapy in localized supradiaphragmatic stages, chemotherapy alone in advanced stages and the abandonment of extensive radiotherapy. However, refractory disease and relapses require the use of more gonadotoxic chemotherapy.

Care from the diagnosis, given the risk of secondary infertility, is an important issue for patients. Concerted multidisciplinary discussions between haematologists, Assisted Reproductive Techniques (ART) teams and surgeons are required to improve the quality of patient information (1), propose measures to preserve fertility adapted to each patient and to assess the consequences of treatment (2).

**Normal Gonadal Structure and Function**

*Women*

The ovaries contain a pool of primordial follicles which attains a maximum level during the 7th month of intrauterine life. The stock of primordial follicles decreases exponentially during life, from 1 to 2 million follicles at birth to 400 000 during early puberty. From 37 years onwards, the stock declines acceleratedly down to a stock of fewer than 1000 follicles on average at the time of the menopause (50.4 years) (3).

The ovarian reserve, namely the number of primordial follicles present at a given age, evolves in line with fertility in women of childbearing capacity. The ovarian cycle is regulated by gonadotropin hormones.

Premature ovarian failure (POF) is defined as the premature (age 40) termination of ovarian function, of peripheral origin (4). The destruction of part or of the entire stock of primordial follicles is the cause of hypergonadotropic amenorrhea defined as the loss of negative feedback. The main consequence of this syndrome is infertility, but women also exhibit symptoms of oestrogen deprivation with hot flushes, vaginal dryness, dyspareunia. There are several causes of POF but the most common is exposure of the ovaries to a toxic substance, particularly a cytotoxic agent.

Thus chemotherapy is responsible for DNA damage that directly affects the ovary. Alkylating agents produce covalent bonds between DNA strands, rendering cleavage impossible during replication and thus blocking division. These lesions induce apoptosis that not only affects the follicle but also the growing population of primordial follicles. The interruption of this signalling pathway leading to apoptosis is currently an interesting way to avert damage to the ovary (5, 6).

*Men*

Spermatogenesis begins in the testes in males during early puberty. It encompasses the entire development process, from spermatogonia (primordial differentiated germ cells) to sperm. This process occurs in the seminiferous tubules and consists of the different stages of differentiation of germ cells and Sertoli cells, the supporting cells which are essential for spermatogenesis. A complete cycle of spermatogenesis takes about 74 days. The eventual restoration of spermatogenesis after treatment depends on the integrity of spermatogonia and their ability to differentiate.
Infertility Risk Factors

- **Patient Characteristics**

  **Women**

  Among women treated for cancer, age, and thus the status of the ovarian reserve before treatment initiation, exert a major impact on the subsequent risk of infertility. For the same treatment, the percentage of POF and the resulting percentage of infertility increases with age. This risk is greatest after 30 years (7, 8). All studies on Hodgkin lymphoma report an impact of age on fertility. A Norwegian study in which the median follow-up (20 years) is higher than in other studies, showed that women under 25 run the same risk of developing POF as women over 30 years but after a much longer interval: 15 years vs. 2 years (9).

  **Men**

  Unlike women, the spermatogonia stock is constant throughout life. This explains why age is not a predictor of infertility in men treated with chemotherapy.

  Studies evaluating the quality of semen at the diagnosis of Hodgkin lymphoma, showed a high percentage of abnormal sperm analyses before treatment. This percentage varies from one study to another. Some authors described up to 80% of abnormal sperm analyses (10). The most recent study is a retrospective study conducted by the EORTC (European Organization for Research and Treatment of Cancer Lymphoma Group) and the GELA (Groupe d’Etude des Lymphomes de l’Adulte). They reported that among 474 patients analyzed, 41% had a normal semen analysis, 49% an intermediate-grade analysis, 7% a poor analysis and 3% of patients were azoospermic, including two who recovered normal sperm parameters after chemotherapy (11). Risk factors are the presence of general symptoms at the time of the diagnosis, especially fever and night sweats and an increased erythrocyte sedimentation rate (ESR). The exact mechanisms are unknown but proinflammatory cytokines are assumed to be implicated. The stage of the disease has no impact.

- **Treatment-related risks**

  **First-line regimen**

  Table 1 presents an overview of the treatment-related risk of infertility.

  In women, the type and dose of chemotherapy and age are the most important risk factors for infertility (7). This risk is greatest after exposure to alkylating agents, with a relative risk of 3.98 compared to an unexposed population. It increases with the cumulative dose.

  The two protocols currently used in Hodgkin lymphoma during first-line therapy are the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen and the escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone) regimen, which differ essentially due to the presence of alkylating agents in the BEACOPP regimen (12). For example, the total dose of cyclophosphamide known to lead to the highest risk of ovarian failure at the end of treatment is 20 grams at 20 years, 9 grams at 30 and 5 grams at 40 years.

  Several studies have investigated the impact of these 2 chemotherapy regimens on fertility. They are all retrospective studies with different objectives (children, the study of hormone assays in the 2 sexes and the study of menstrual cycles and ultrasound in women).

  Thus the German Study Group published in 2005 a paper on the recovery of normal menstrual cycles (which is one aspect of ovarian function) after BEACOPP, COPP/ ABVD or ABVD (13). After a median of 3.2 years, 19.3% of the 405 women contacted had amenorrhea. The
main risk factors identified in the multivariate analysis were the type of treatment, with a higher risk for amenorrhea during treatment with the escalated BEACOPP regimen than with the baseline BEACOPP, ABVD or COPP/ABVD, the patient’s age (more or less than 30 years), the stage of the disease and surprisingly, the absence of oral contraception. Decanter et al. compared the anti-Müllerian hormone (AMH) assay in patients treated with ABVD and in patients treated with chemotherapy containing alkylating agents. The rate of AMH decreased significantly in the 2 groups but at one year, the ABVD group recovered a normal AMH rate whereas it remained depleted in the other group (14). A Norwegian study published in 2007 and a French study published in 2003, investigating the number of pregnancies per woman, confirmed that the type of treatment, and in particular the dose of alkylating agents, and age were the two main risk factors for infertility (15, 16). Pregnancies after chemotherapy did not give rise to more complications than in the general population (17). Finally, two other studies confirmed the safety of ABVD with a birth rate comparable to that of the general population regardless of the patient’s age or the number of treatment courses (18, 19).

Among men, the risk of infertility depends on the treatment used. The risk is low after radiotherapy alone if pelvic radiation is avoided or chemotherapy without alkylating agents. It increases significantly when alkylating agents are used. The incidence of azoospermia is lower after ABVD compared to ABVD/COPP or MOPP (20). Van der Kaaij et al analyzed follicle-stimulating hormone (FSH) levels and reported that after a median time of 19 months, recovery of fertility occurred in 82% of patients treated without alkylating chemotherapy, compared to only 30% of those treated with alkylating agents, with a median time to recovery of 27 months ($P < .001$) (21).

After BEACOPP, abnormal sperm or an increase in serum FSH levels were observed in 90 to 100% of cases. There is no difference between baseline BEACOPP and escalated BEACOPP (22). After COPP/ABVD, the infertility rate is between 60-91% and varies depending on the number of treatment courses. After ABVD, the infertility rate is 0 to 8% and after chemotherapy and pelvic radiotherapy, an infertility rate of 2 to 11% has been reported (23, 24). Alkylating agents are the main risk factor for infertility and that risk is proportional to dose. The recovery of normal exocrine testicular function mainly depends on the dose of alkylating agents and may take several years.

A Norwegian study reported 269 men treated for Hodgkin lymphoma, between 1971 and 1998 (15). From 1985 to 1990, primary chemotherapy with MVPP/ChIVPP (mechlorethamine, vinblastine, procarbazine, prednisone/chlorambucil, vinblastine, procarbazine, prednisone) was gradually replaced by ABOD (doxorubicin, bleomycin, vincristine, dacarbazine) or EBVP (epirubicin, vinblastine, procarbazine, prednisone) for limited disease. At relapse, patients were treated with noncross-resistant chemotherapy, or from 1990 with high-dose chemotherapy with autologous stem cell support (HDT). Fractionated total body irradiation (TBI) with high-dose cyclophosphamide was used as a conditioning regimen for HDT until 1995, and was subsequently changed to chemotherapy alone (BEAC/BEAM). Among 120 males (45%) who reported having attempted post-treatment parenthood, 76 (63%) had been successful without using ARTs. In addition, 10/13 males achieved post-treatment parenthood with the use of ARTs after 15 years of follow-up. The percentage of fatherhood may increase with progress in in vitro fertilization techniques. Indeed, with progress in ARTs, even very oligozoospermic patients may benefit from fertilization techniques such as ICSI (IntraCytoplasmic Sperm Injection).
Treatments of refractory lymphoma or relapses

Second-line chemotherapy
The main protocols used are DHAP (dexamethasone, high-dose cytarabine, cisplatin) (25), ICE (ifosfamide, carboplatin, etoposide)(26), MINE (methyl-glioxal, ifosfamide, vinorelbine, etoposide) (27), GVD (gemcitabine, vinorelbine, liposomal doxorubicin) (28). Most teams use them, but the risk in terms of fertility has not been evaluated.

Hematopoietic cell transplantation
The risk of infertility has not been extensively studied after transplantation. Several studies reported that the regimens used for allogeneic stem-cell conditioning cause the most severe damage, especially in case of total body irradiation (TBI), with POF and infertility almost constantly occurring in adults and in up to 81% of cases in children (29, 30). Pregnancies have been reported after conditioning with BEAM (carmustine, etoposide, cytarabine, melphalan) and autologous transplantation. A recent report from the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) concluded that some patients who received TBI and/or myeloablative conditioning can preserve their fertility. The study described 83 pregnancies in female haematopoietic cell transplantation (HCT) recipients and 95 pregnancies in female partners of male HCT recipients (31).

Radiation
The risk depends on the irradiated volume and dose. After radiotherapy above the diaphragm (mantle-field), the dose to the gonads is approximately 0.1%. A change in ovarian function is reported after a dose of 1.5 Gy in patients after 40 years. After 2.5 to 5.0 Gy, 30 to 40% of women between 15 and 40 years become infertile and over 90% of patients after 40 years (32). A decrease in the sperm count was observed after a dose of 0.15 Gy, and a risk of sterilisation may occur after a dose of 1-2 Gy.
Sub-diaphragmatic radiation has been abandoned for initial treatment, and indications are rare and specific. Total body irradiation is used for selected patients undergoing autologous transplantation, and in some cases of dose-reduced conditioning followed by allogeneic stem cell transplants in relapses.

Assessment of fertility
- Ovarian reserve assessment
The assessment of the ovarian reserve is used to estimate the risk of infertility in patients treated for cancer. This assessment is based on a series of arguments.

Clinical evidence
- Menstrual cycles
After chemotherapy, recovery of normal menstrual cycles does not guarantee normal fertility, but amenorrhea is a strong negative predictor of fertility. Indeed, in several studies, patients with normal cycles had abnormal hormonal markers and abnormal transvaginal ovarian ultrasound examinations. The presence of transient amenorrhea after treatment was demonstrated to be a risk factor for subsequent infertility.

Paraclinical evidence
- Endocrine Profile
There are several hormone assays. FSH is normally elevated in cases of impaired fertility. However, most studies agree that a normal FSH determination does not exclude ovarian dysfunction. The Anti-Müllerian hormone (AMH) produced by growing follicles declines with age and is undetectable after menopause. Its level parallels that of the number of primordial follicles and seems to be the most informative determination (33).
authors recommend the determination of inhibin B hormone which is secreted by the follicles recruited during the ovarian cycle. This hormone is involved in the negative regulation of FSH. As the level of inhibin B decreases with age, an increase in FSH levels through the loss of negative feedback is also observed.

- Transvaginal Ultrasound
Numerous studies have demonstrated the usefulness of transvaginal ultrasound, particularly at day 3 of the menstrual cycle. It provides two essential parameters: the measurement of the ovarian volume and the follicular count which is the number of follicles between 2 and 10 mm in diameter, which correspond to small antral follicles. These two elements correlate significantly with ovarian reserve and fertility. In patients with amenorrhea, the usefulness of this technique is not proven (34). Consequently, there are no standard recommendations. The diagnosis of POF is therefore based on a body of clinical and laboratory evidence. Most authors combine the estimation of AMH and transvaginal ultrasound.

• Male fertility assessment
The essential test is the semen analysis. It permits a study of the sperm count, shape, vitality and mobility. This is an excellent reflection of exocrine testicular function and of fertility. As a cycle of spermatogenesis takes three months, it is pointless to conduct the test too soon after treatment. It can be repeated and often results improve over time. Some hormone assays can also provide information on gonadal function. FSH, which is secreted by the pituitary gland, rises if testicular tissue sustains injury, due to loss of negative feedback. Inhibin B is secreted by Sertoli cells and its level is low in cases of spermatogenesis dysfunction. It would be a better marker than FSH (35).

Different fertility preservation methods
• Women
With an improvement in the prognosis for patients with Hodgkin lymphoma, the management of secondary infertility treatment has become an important goal. Several techniques are under development and require close collaboration between oncology and ART teams.

For the time being, it has been established that the chemotherapy in use is a known risk for future infertility. Several options are available depending on the patient’s age, the presence or absence of a partner and the patient’s wishes (36, 37) (Table 2).

In Vitro Fertilization (IVF) for embryo cryopreservation
In ART centres, IVF is performed in many infertile patients and good results are obtained. After ovarian stimulation, mature oocytes are collected and fertilized in vitro. The resulting embryos are frozen. Human embryo freezing and thawing protocols are well established and used to obtain satisfactory embryo survival. At the appropriate time, the embryo(s) is/are implanted and pregnancy can be completed. The pregnancy rate per embryo transfer is approximately 18%. However, this technique is possible only in puberal women with a stable partner. Moreover, ovarian stimulation for 9-14 days, starting on the 2nd or 3rd day of menses, can take 4-6 weeks, depending on the time of menses. The possibility of delaying the start of treatment should be discussed but this is dependent on the stage of the lymphoma and on the patient’s wishes, especially in relapse cases or if intensification is proposed.

Mature oocyte cryopreservation
This technique, equivalent to the freezing of sperm, appears to be the most logical for women of childbearing age. However, the results are still disappointing. After ovarian stimulation
which takes 4 to 6 weeks, the oocytes are frozen at the metaphase of a second meiotic division (MII). After thawing they are mixed in vitro with the partner’s sperm and the resulting embryos are then placed in the uterine cavity of the patient. The first pregnancy was reported in 1986. However, the oocytes are fragile and are often altered by the freezing-thawing cycle. Until recently, the pregnancy rate obtained was less than 3% per frozen oocyte. Two new techniques have increased this percentage:

- Fertilization of oocytes by IntraCytoplasmic Sperm Injection (ICSI)
- The Vitrification Process (ultra-rapid freezing) significantly reduces cell loss. The pregnancy rate attains 6.8% with vitrified oocytes (38).

**Cryopreservation of ovarian tissue (CPOT)**

This is a promising technique but still recent (39). The principle is to remove a whole ovary by laparoscopy. It is then prepared in the laboratory. The cortex is isolated in order to freeze ovarian cortex segments according to a carefully established protocol in the presence of cryoprotectants. Many follicles, mostly primordial, are frozen.

Oocyte maturation is therefore required for fertilization. There are three theoretical methods of maturation. In vitro maturation and xenografting are currently only research avenues. Autografting of frozen-thawed ovarian cortex segments is the technique currently used. After thawing, the ovary is implanted either in an orthotopic position, i.e. in the pelvic cavity, or in a heterotopic position (in the forearm, in the abdominal wall ...).

About thirty attempts have been published, including 11 patients treated for Hodgkin lymphoma (40). In these articles, all the women recovered ovarian endocrine function with a return of menstruation, an improvement of symptoms such as hot flashes and an improvement of hormone assays. However, to date, only 12 full-term pregnancies succeeding to 13 live births, have been reported worldwide (including 4 in patients with Hodgkin lymphoma), with the occasional need for ovarian stimulation and, in cases of heterotopic reimplantation, routine in vitro fertilization (IVF) (41-43). The results of this technique are therefore still uncertain, which is what the clinician should clearly explain to patients. However CPOT is the only feasible technique in children and prepuberal adolescents (44).

The main risk of this procedure is possibly reintroducing cancer cells. In the case of Hodgkin lymphoma, the risk is very low (ovarian invasion was found in <5% of autopsy series). Only one team has reported a case of disease invading a specific ovary removed from a young woman. This was detected at the histological analysis. Such verification is essential before pathological freezing. A pelvic relapse has never been reported after ovarian implantation (45).

The other major drawback of the CPOT is the amputation of 50% of the ovarian reserve. Thus, there is a risk of accelerating the process of POF, although this risk is not clear (46). It should therefore only be proposed to women undergoing treatment with a risk of infertility of nearly 100% as is the case with transplant conditioning. After conventional chemotherapy regimens, even those containing alkylating agents, this risk is modulated according to the patient’s age and the dose. As mentioned above, young women are likely to recover normal ovarian function and to be able to complete spontaneous pregnancies.

**Analogues of LH-RH**

The hypothalamus secretes GnRH or LHRH in a pulsatile manner. This hormone acts on specific receptors in pituitary gonadotroph cells that in turn secrete LH and FSH. Continuous
administration of LHRH (or GnRH) causes desensitization of the hypothalamic-pituitary axis which, when prolonged, induces biochemical castration and a collapse of FSH and LH. Analogues of LHRH are substrates of decapptide GnRH, the natural molecule. They are 50- to 200-fold more potent than the natural peptide. Their administration therefore neutralises the hypothalamic-pituitary axis. This chemical menopause inhibits the initiation of growth of primordial ovarian follicles, which would protect them from the cytotoxic action. This technique is highly contested. For the time being, two randomised trials have demonstrated an improvement in tests reflecting the ovarian reserve in the treated arm, but there is an equivalent rate of spontaneous pregnancies in both arms (47, 48). Two other studies (the most recent was conducted by the German group) that randomised oral contraceptives and GnRH in patients treated with escalated BEACOPP, were unable to evidence any efficacy of GnRH which did not improve the hormone assays (49, 50). Analogs of LHRH are therefore not recommended in the absence of studies demonstrating their effectiveness. For women who experience premature menopause, hormone replacement therapy may reduce the risks of oestrogen deficiency, such as osteoporosis.

Men

In adults and adolescents after puberty

Two techniques exist for sperm collection. The self-preservation of ejaculated semen is the most current. The semen is collected by masturbation and analyzed according to WHO criteria. The ejaculate is then diluted with cryoprotectant, packed in straws, frozen in liquid nitrogen vapour and placed in tanks for long-term storage in liquid nitrogen. Usually 2 to 4 collections are necessary and an average of 24 straws are stored for each patient. In case of azoospermia, a testicular biopsy can be performed which allows sperm to be obtained in approximately half of the cases.

In most patients, even if the quality of the sperm is low, it can be used for ART. If the patient has secondary infertility due to cytotoxic agents, the technique will be chosen based on the number of flakes, the number of motile spermatozoids per straw, an eventual improvement in the sperm test after treatment and the results of the female partner’s tests. The different techniques available are:

- Intrauterine Insemination
- Simple in vitro fertilization
- In vitro fertilization with an intra-cytoplasmic sperm injection (ICSI): ICSI allowed ART to be proposed to very oligospermic patients.

One in every two patients in care for ART will have a child. Currently the recommendation is to provide self-preservation of ejaculated semen for patients treated with the BEACOPP regimen or before salvage treatment for relapse, and it remains optional for patients treated with ABVD, considering the low risk of infertility after the ABVD regimen. Most patients recover normal spermatogenesis after ABVD, often as long as 6 to 18 months later, and the Centre d’Etudes et de Conservation des Oeufs et du Sperme (CECOS – Egg and Sperm Conservation Centers) asks patients to decide whether or not to continue conservation first.

In the pre-pubescent boy

Several techniques are being tested. Cryopreservation of immature testicular tissue can lead to a transplant and in case of recovery of spermatogenesis, the collected gametes could be used in ART (51). A technique that has already been tested in humans is the cryopreservation of germ stem cells which are then reimplanted in the testis. It is still experimental, but would avoid recourse to ART (52). In vitro production by induction of gametes from embryonic stem cells is still being tested in animals.
Conclusion
The risk of infertility related to chemotherapy must be discussed with patients at the time of the diagnosis. In both sexes, one of the main risk factors for infertility is the type of chemotherapy used and in particular the dose of alkylating agents. In women, age below 30 years is a protective factor and thus the ovarian reserve also plays a major role.
In figure 1, we propose a decision algorithm for managing the handling of fertility preservation that can be presented to patients. Among adults and adolescents after puberty, semen cryopreservation is proposed before first-line treatment with BEACOPP or salvage treatment for relapse, and it is optional in cases of localized Hodgkin lymphoma treated with ABVD and radiotherapy. In women, fertility preservation is not systematically proposed before first-line treatment with ABVD; however the risk of POF increases with age. Preservation methods can be offered to patients over 35 years, and decided according to the patient’s wishes. ARTs are not routinely recommended for patients receiving ABVD in their early twenties to mid-thirties. For women receiving BEACOPP or the BEAM conditioning regimen and an autologous transplant, an ART consultation should be offered so that they can make a personalised decision, given that these treatments do not systematically cause sterility. For women with a stable partner, in vitro fertilization for embryo cryopreservation is a standard procedure but it can be offered to only a small number of patients and requires delayed treatment initiation. Oocyte cryopreservation remains experimental, although it is increasingly being developed with new cryopreservation techniques that improve the results and may soon make it more recommendable. Ovarian tissue cryopreservation is still experimental, it should only be proposed to women undergoing treatment with a high risk of infertility. The benefit-to-risk ratio must be discussed according to the patient’s age and wishes, and also the possibility of delaying treatment initiation. Optimal management requires multidisciplinary collaboration between haematologists and Assisted Reproductive Techniques teams.

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AUTHORSHIP AND DISCLOSURES
SH, CF and CP wrote the manuscript. All authors approved the final version of the manuscript and declare that they have no conflicts of interest and no competing financial interests.
References


Table 1. Treatment-related risk of infertility for patients with Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>No. Pts</th>
<th>Disease</th>
<th>Follow-up</th>
<th>End-point</th>
<th>Treatment</th>
<th>Results</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behringer et al. 2005(13)</td>
<td>Women</td>
<td>405</td>
<td>HL</td>
<td>3.2 years.</td>
<td>Amenorrhea</td>
<td>Radiotherapy</td>
<td>6.3%</td>
<td>Alkylating agent, Age, Disease stage</td>
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<td>ABVD, 2COPP/ABVD, 4COPP/ABVD, 8 BEACOPP, 8BEACOPPesc</td>
<td>3.9%</td>
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<tr>
<td>Decanter et al. 2010(14)</td>
<td>Women</td>
<td>30</td>
<td>HL and NHL</td>
<td>1 year.</td>
<td>AMH dosage</td>
<td>ABVD, Non ABVD(1)</td>
<td>Normal Decrease</td>
<td></td>
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<tr>
<td>Hodgson et al. 2007(18)</td>
<td>Women attempting pregnancy</td>
<td>36</td>
<td>HL</td>
<td>1 year.</td>
<td>Parenthood</td>
<td>ABVD</td>
<td>Same fertility rate as controls</td>
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<tr>
<td>Brusamolino et al. 2006(19)</td>
<td>Women</td>
<td>67</td>
<td>HL</td>
<td>10 years.</td>
<td>Amenorrhea</td>
<td>ABVD</td>
<td>Fertility preserved</td>
<td>10 became pregnant</td>
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<td>Franchi-Rezgui et al. 2003(16)</td>
<td>Women attempting pregnancy</td>
<td>84</td>
<td>HL and NHL</td>
<td>8 years</td>
<td>Parenthood</td>
<td>ABVD(2)</td>
<td>37%: preserved fertility</td>
<td>40%: POF, 23%: relative fertility</td>
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<td>18%</td>
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<td>Men</td>
<td>38</td>
<td>HL</td>
<td>34 months.</td>
<td>FSH level, Sperm count</td>
<td>ABVD, COPP/ABVD</td>
<td>Normal FSH level, Normal FSH level</td>
<td>Alkylating agent</td>
</tr>
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Azoospermia only in COPP/ABVD arm.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Number</th>
<th>HL</th>
<th>Duration</th>
<th>FSH Level</th>
<th>Without alkylating agent</th>
<th>With alkylating agent</th>
<th>Recovery of fertility</th>
<th>Dose of alkylating agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Kaaij et al. 2007(21)</td>
<td>Men</td>
<td>349</td>
<td>HL</td>
<td>26 months</td>
<td>FSH level</td>
<td>Without alkylating agent</td>
<td>With alkylating agent</td>
<td>Recovery of fertility</td>
<td>Dose of alkylating agent</td>
</tr>
<tr>
<td>Sieniawski et al. 2008(23)</td>
<td>Men</td>
<td>112</td>
<td>HL</td>
<td>17.4 months</td>
<td>Azoospermi a</td>
<td>Radiotherapy</td>
<td>ABVD</td>
<td>2COPP/ABVD</td>
<td>4COPP/ABVD</td>
</tr>
<tr>
<td>Hobbie 2005(24)</td>
<td>Men</td>
<td>11</td>
<td>HL</td>
<td>6.5y</td>
<td>Azoospermi a</td>
<td>COPP/ABV</td>
<td>63%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HL : Hodgkin lymphoma, Non Hodgkin Lymphoma: COPP (cyclophosphamide, vincristine, procarbazine, prednisone), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone);

(1) Non ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) group: R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), ACVPB (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone), BEACOPP, BEAM (carmustine, etoposide, aracytine, melphalan), MINE (methyl-glioxal, ifosfamide, vinorelbine, etoposide)

(2) MOPP/ABV (mechlorethamine, vincristine, procarbazine, prednisone/doxorubicin, bleomycin, vinblastine), ABVPP (doxorubicin, bleomycin, vinblastine, procarbazine, prednisone), ACVPB, ECVPB (epirubicin, cyclophosphamide, vindesine, bleomycin, prednisone), CHOP, MOPP (mechlorethamine, vincristine, procarbazine, prednisone), BEAM, IVAM (ifosfamide, etoposide, aracytine, methotrexate)

(3) LowChem: Low = ABO(V)D (doxorubicin, bleomycin, vincristine, dacarbase), EBVD (epirubicin, bleomycin, vinblastine, dacarbase)

MedChem : Medium Chemotherapy = ChIVPP (chlorambucil, vinblastine, procarbazine, prednisone) ≤4 courses, MVPP (mechlorethamine, vinblastine, procarbazine, prednisone) ≤4 courses, CHOP, MIME (methyl-glioxal, ifosfamide, methotrexate, etoposide); HDChemo : High-dose Chemotherapy = ChIVPP > 4 courses, MVPP > 4 courses, ASCT support BEAC/BEAM

(4) Chemotherapy without alkylating agents : ABVD, EBVP (epirubicin, bleomycin, vinblastine, prednisone); Chemotherapy with alkylating agents: MOPP, MOPP/ABV, BEACOPP.
<table>
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<tr>
<th>Method</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vitro</em> fertilization for embryo cryopreservation</td>
<td>Accessible technique&lt;br&gt;Good pregnancy rate</td>
<td>Ovarian stimulation&lt;br&gt;Puberal women&lt;br&gt;Partner</td>
</tr>
<tr>
<td>Mature oocyte cryopreservation</td>
<td>No need for maturation</td>
<td>Ovarian stimulation&lt;br&gt;Puberal women&lt;br&gt;Low pregnancy rate</td>
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<tr>
<td>Cryopreservation of ovarian tissue</td>
<td>No previous ovarian stimulation&lt;br&gt;Numerous immature oocytes</td>
<td>Amputation of 50% of the ovarian reserve&lt;br&gt;Recent technique&lt;br&gt;Oocyte maturation&lt;br&gt;Risk of reintroducing cancer cells after autografting</td>
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</table>
Figure 1. Decision-algorithm to manage the handling of fertility preservation in first-line treatment and for refractory/relapsing patients.
First line treatment

ABVD
- Women
  - No particular measures monitoring
- Men
  - Sperm cryopreservation to be discussed

BEACOPP
- Women
  - ART consultation
- Men
  - Sperm cryopreservation systematic

Refractory / relapses
- High-dose chemotherapy
  - Bone marrow transplantation

- Women
  - Systematic ART consultation
  - Consider fertility preservation
- Men
  - Systematic sperm cryopreservation
    - If already done: check quality

Depending on the patient's age, the presence or absence of a partner, the patient's wishes and the time to treatment