"How to preserve fertility before chemotherapy"

Donnez, Jacques ; Jadoul, Pascale ; Donnez, Olivier ; Squifflet, Jean-Luc ; Gilliaux, Sébastien ; Dolmans, Marie-Madeleine

Abstract
Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of premenopausal women with cancer. Unfortunately, aggressive chemo- and radiotherapy can result in the loss of both endocrine and reproductive functions, leading to premature menopause and infertility. It is thus our duty to evaluate the effects of specific cancer treatments on fertility and discuss fertility preservation options with these young women prior to cancer treatment. The different cryopreservation options available for fertility preservation in cancer patients are embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation. There is conflicting evidence on the use of GnRH analogs to preserve fertility in women undergoing chemotherapy, and GnRH analogs are not indicated for patients undergoing radiotherapy. The only established method of fertility preservation is embryo cryopreservation, but this requires the patient to be o...

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Introduction
According to previous reports, more or less 700,000 new cancer cases are expected every year amongst the female population of the United States.1 About 8% of these women are under the age of 40. Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of premenopausal women with cancer. Unfortunately, aggressive chemo- and radiotherapy can result in the loss of both endocrine and reproductive functions, leading to premature menopause and infertility. It is thus our duty to evaluate the effects of specific cancer treatments on fertility and discuss fertility preservation options with these young women prior to cancer treatment. The different cryopreservation options available for fertility preservation in cancer patients are embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation. There is conflicting evidence on the use of GnRH analogs to preserve fertility in women undergoing chemotherapy, and GnRH analogs are not indicated for patients undergoing radiotherapy. The only established method of fertility preservation is embryo cryopreservation, but this requires the patient to be of pubertal age, have a partner, and be able to undergo a cycle of ovarian stimulation. Cryopreservation of ovarian tissue is the only option available for prepubertal girls, and for woman who cannot delay the start of chemotherapy. Twenty-five cases of orthotopic reimplantation of cryopreserved ovarian tissue have so far been reported and six live births have been achieved, yielding a pregnancy rate of almost 25%. With all the advances in ovarian tissue cryobanking and reproductive technology, fertility preservation is now a real possibility for patients whose gonadal function is threatened by radio- or chemotherapy. For this reason, it should be a medicolegal obligation for gynecologists, oncologists and pediatricians to systematically propose cryopreservation before initiating cancer therapy that could impair future fertility.

Summary
Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of premenopausal women with cancer. Unfortunately, aggressive chemo- and radiotherapy can result in the loss of both endocrine and reproductive functions, leading to premature menopause and infertility. It is thus our duty to evaluate the effects of specific cancer treatments on fertility and discuss fertility preservation options with these young women prior to cancer treatment. The different cryopreservation options available for fertility preservation in cancer patients are embryo cryopreservation, oocyte cryopreservation and ovarian tissue cryopreservation. There is conflicting evidence on the use of GnRH analogs to preserve fertility in women undergoing chemotherapy, and GnRH analogs are not indicated for patients undergoing radiotherapy. The only established method of fertility preservation is embryo cryopreservation, but this requires the patient to be of pubertal age, have a partner, and be able to undergo a cycle of ovarian stimulation. Cryopreservation of ovarian tissue is the only option available for prepubertal girls, and for woman who cannot delay the start of chemotherapy. Twenty-five cases of orthotopic reimplantation of cryopreserved ovarian tissue have so far been reported and six live births have been achieved, yielding a pregnancy rate of almost 25%. With all the advances in ovarian tissue cryobanking and reproductive technology, fertility preservation is now a real possibility for patients whose gonadal function is threatened by radio- or chemotherapy. For this reason, it should be a medicolegal obligation for gynecologists, oncologists and pediatricians to systematically propose cryopreservation before initiating cancer therapy that could impair future fertility.

How to preserve fertility before chemotherapy

J. Donnez, P. Jadoul, O. Donnez, J. Squifflet, S. Gilliaux, M-M. Dolmans

Key words
Cryopreservation, ovary, fertility, radiotherapy, chemotherapy, transplantation

Introduction
According to previous reports, more or less 700,000 new cancer cases are expected every year amongst the female population of the United States.¹ About 8% of these women are under the age of 40. Advances in the diagnosis and treatment of childhood, adolescent and adult cancer have greatly increased the life expectancy of premenopausal women with cancer. Indeed, aggressive chemo- and radiotherapy, as well as bone marrow transplantation, are now able to cure more than 90% of girls affected by childhood malignancies, but have resulted in a growing population of adolescent and adult long-term survivors of childhood malignan-
Cyclophosphamide is the agent most commonly implicated in causing damage to oocytes and granulosa cells in a dose-dependent manner. A combination of various chemotherapeutic agents further increases gonadal toxicity. This follicular destruction generally results in loss of both endocrine and reproductive function, depending on the dose and the age of the patient. Indeed, Larsen et al. reported a 4-fold increased risk of POF in teenagers treated for cancer, and a risk increased by a factor of 27 in women between 21 and 25 years of age. Procarbazine has recently been described as high risk for inducing premature menopause. Ten years after treatment for Hodgkin’s lymphoma, the risk of premature menopause was 84% after high cumulative doses (> 8.4 g/m²), and 15% after low doses (≤ 4.2 g/m²) of procarbazine. The authors concluded that, as long as alkylating agents are used to cure Hodgkin’s lymphoma, premature menopause will remain a common adverse effect, with various clinical implications.

The gonadotoxicity of radiotherapy has been stated that a dose of 5-20 Gy administered to the ovary is sufficient to completely impair gonadal function, whatever the age of the patient. The dose of radiation required to destroy 50% of the oocyte reserve has been found to be < 2 Gy. Moreover, uterine irradiation at a young age reduces adult uterine volume. Radiation doses between 14 and 30 Gy have been reported to result in uterine dysfunction. The practitioner should be aware of this effect of radiotherapy on the uterus, which could interfere with the implantation capacity of embryos.

Intensive chemotherapy and/or total body irradiation (TBI) required before bone marrow transplantation (BMT) constitute the treatment combination presenting the greatest risk of POF. Indeed, the high doses of chemotherapy (commonly using the highly cytotoxic cyclophosphamide/busulfan regimen) and/or radiotherapy lead to subsequent ovarian failure in almost all cases, children and adults alike. The risk of POF was estimated to be 92% in the study by Meirow and Nugent, and 100% in an earlier study by Teinturier et al. A large retrospective survey of pregnancy outcomes after hematopoietic stem cell transplantation (HSCT) (peripheral blood or BMT) involving 37,362 patients revealed that only 0.6% of patients conceived after autologous or allogenic SCT. It is thus obvious that high doses of alkylating agents, irradiation and advancing age increase the risk of gonadal damage.

## Table 1. Cytotoxic agents according to degree of gonadotoxicity.

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Low/no risk</th>
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<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Adriamycin (doxorubicin)</td>
<td>Methotrexate</td>
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<tr>
<td>Busulfan</td>
<td>Cisplatin</td>
<td>Bleomycin</td>
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<tr>
<td>Melphalan</td>
<td>Carboplatin</td>
<td>5-Fluorouracil</td>
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<tr>
<td>Chlorambucil</td>
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<td>Actinomycin D</td>
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<td>Dacarbazine</td>
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<td>Mercaptopurine</td>
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<td>Procarbazine</td>
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<td>Vincristine</td>
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<td>Ifosfamide</td>
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<td>Thiotepa</td>
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<tr>
<td>Nitrogen mustard</td>
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### Gonadotoxicity of radiotherapy

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### Gonadotoxicity of combined intensive chemotherapy and total body irradiation (TBI)

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### Fertility preservation in cancer patients: different cryopreservation options

#### Embryo cryopreservation

Figure 1. Biopsies of ovarian cortex are removed by laparoscopy for cryopreservation. The superficial cortex harvests the primordial follicles.
Embryo cryopreservation should be considered the first-line approach to fertility preservation, but this option requires the patient to be of pubertal age, have a partner or use donor sperm, and be able to undergo a cycle of ovarian stimulation, which is not possible when chemotherapy has to be initiated immediately or when stimulation is contraindicated according to the type of cancer.\(^\text{14}\) For women whose cancer therapy can be delayed, IVF with embryo cryopreservation should be offered. This should be carried out before chemotherapy and not after first-line chemotherapy, as the ovarian response would be reduced dramatically.\(^\text{15}\)

Cryopreservation of oocytes
Cryopreservation of oocytes can be performed in post-pubertal patients without a partner, if they are able to undergo a stimulation cycle. The efficacy of the technique is still low with slow cooling techniques, because mature oocytes are sensitive to temperature changes. Delivery rates of 1-5% have been obtained per frozen–thawed oocyte.\(^\text{16,17}\) However, since the recent introduction of oocyte vitrification, delivery rates have almost doubled per thawed oocyte.\(^\text{17}\) Human oocytes are usually cryopreserved at a mature (metaphase II) stage. Although immature (germinal vesicle) oocytes are more cryoresistant, the continued inefficiency of *in vitro* maturation (IVM) protocols results in a final yield of mature oocytes that is similar to that obtained with slow-cooled cryopreserved metaphase II oocytes.\(^\text{18}\)

**Ovarian tissue cryopreservation**
For patients who need immediate chemotherapy, cryopreservation of ovarian tissue is the only possible alternative and should be considered as an emergency procedure in order not to delay chemotherapy. Ovarian tissue cryopreservation should be undertaken before chemotherapy and written informed consent must be obtained. By laparoscopy, five biopsy samples are taken (Figure 1). Removal of the whole ovary is usually not an option because one can never exclude recovery of ovarian function after chemotherapy. Indeed, POF after chemotherapy is dependent on age, drug used and dose given, and does not occur in all cases.

The main aim of this strategy is to reimplant cortical ovarian tissue into the pelvic cavity (orthotopic site) or a heterotopic site like the forearm or the abdominal wall once treatment is completed and the patient is disease-free (Figure 2).\(^\text{19-30}\)

**Indications for ovarian tissue cryopreservation**
In the field of oncological indications for ovarian tissue cryopreservation, there have been no major modifications since the review by Donnez *et al* published in 1998 (Table 2).\(^\text{19}\) The most frequent

| Table 2. Indications for cryopreservation of ovarian tissue in case of malignant and non-malignant diseases |
|---|---|---|---|
| **Malignant diseases** | **Extrapelvic disease** | **Pelvic disease** | **Gynecological** |
| **Systemic disease** | Bone cancer (osteosarcoma) | Pelvic sarcoma | Early cervical carcinoma |
| Hodgkin’s disease | Ewing’s sarcoma | Sacral osteoblastoma | Early vaginal carcinoma |
| Non-Hodgkin’s lymphoma | Breast cancer | Rhabdomyosarcoma | Early vulval carcinoma |
| Leukemia | Melanoma | Sacral tumors | Stage IA ovarian carcinoma |
| Medulloblastoma | Neuroblastoma | Rectosigmoid tumors | Borderline ovarian tumors |
| **Non-malignant diseases** | **Risk premature menopause** | **Bone marrow transplantation** |
| Uni/bilateral oophorectomy | Turner’s syndrome | Benign hematological diseases: sickle cell anemia, thalassemia major, aplastic anemia |
| Benign ovarian tumors | Family history | Autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, Behçet’s disease, Wegener’s granulomatosis |
| Severe and recurrent endometriosis | Autoimmune diseases | Autoimmune diseases unresponsive to immunosuppressive therapy |
| BRCA1 and BRCA2 mutation carriers | | | |

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**Table 2. Indications for cryopreservation of ovarian tissue in case of malignant and non-malignant diseases**

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indications in our department are hematological diseases (Hodgkin’s, non-Hodgkin’s lymphoma, leukemia) and breast cancer, which represent respectively 44.3% and 22% of cryopreservation cases. Cryopreservation should not be reserved solely for women with malignant disease, but also when hematopoietic stem cell transplantation (HSCT) is indicated for non-malignant disease.22 Indeed, HSCT has been increasingly used in recent decades for non-cancerous diseases, such as benign hematological disease (sickle-cell anemia, thalassemia major and aplastic anemia) and autoimmune diseases previously unresponsive to immunosuppressive therapy (systemic lupus erythematosus (SLE), autoimmune thrombocytopenia). Other benign diseases, such as recurrent ovarian endometriosis or recurrent ovarian mucinous cysts, are also indications for ovarian cryopreservation. Patients undergoing oophorectomy for prophylaxis may potentially benefit from ovarian cryopreservation as well.

Is reimplantation of cryopreserved ovarian tissue successful?
Twenty-five cases of autografting of cryopreserved tissue to orthotopic sites have so far been reported and six live births have been achieved, yielding a pregnancy rate of about 25%. In 1997, the first successful transplantation of cryopreserved ovarian tissue resulting in a pregnancy and live birth was reported.20 A 25-year-old woman presented with clinical stage IV Hodgkin’s lymphoma after which ovarian tissue cryopreservation was undertaken before chemotherapy. After laparoscopy, the patient received hybrid chemotherapy (MOPP-ABVB) followed by supradiaphragmatic radiotherapy (38 Gy). In 2003, once the patient had been declared completely disease-free, transplantation went ahead (see Donnez et al, 2004, for techniques). A large strip and 35 small cubes of frozen-thawed ovarian tissue were implanted into a furrow created by the peritoneal window very close to the ovarian vessels and fimbria on the right side (Figure 3). Four months after transplantation, a laparoscopy was carried out to check the viability of the orthotopic graft and to reimplant the remaining 32 ovarian cortical cubes. From 5 to 9 months after reimplantation, concentrations of FSH, 17 β-estradiol and progesterone showed the occurrence of ovulatory cycles. At 11 months, the patient became pregnant and subsequently delivered a healthy baby.20 As described in 2006, five other cases of reimplantation using the same technique were performed.22 Ovarian cortical pieces measuring 10 x 4-5mm were grafted onto the remaining ovary after the cortex of this ovary had been removed, either by laparotomy or laparoscopy (Figure 4A and 4B).
By analyzing these 6 cases, some important points may be raised. In all cases, it took between 4 ½ and 5 months after reimplantation before a follicle could be seen. The process of folliculogenesis takes from 4 to 6 months, during which time the oocyte and surrounding somatic cells undergo a series of changes that eventually result in the development of a large antral follicle, capable of producing a mature oocyte. This time interval between implantation of cortical tissue and the first estradiol peak is also consistent with data obtained from sheep and human beings, although some variations may be observed.

Six live births have so far been reported worldwide among 25 transplantations, giving a pregnancy rate of about 25% in women who should have been infertile after chemotherapy. In 2005, Meirow et al. published a live birth after orthotopic autotransplantation of cryopreserved ovarian tissue in a patient with POF after chemotherapy. Eight months after orthotopic transplantation, the patient spontaneously menstruated. Nine months after transplantation, the patient experienced a second spontaneous menstrual period. After a modified natural cycle, a single mature oocyte was retrieved and fertilized. Two days later, a four-cell embryo was transferred. The patient became pregnant from this embryo transfer and delivered a healthy baby weighing 3000g.

Demeestere et al. reported a pregnancy after natural conception in a woman who had undergone orthotopic and heterotopic transplantation of cryopreserved ovarian tissue. They observed follicular development in all three transplantations sites: large follicles in the ovarian site, only one dominant follicle in the peritoneal site and follicles smaller than 13mm in the heterotopic site. Detectable hCG levels and ultrasonography confirmed the presence of a viable intrauterine pregnancy. Unfortunately, this pregnancy, obtained by natural conception, ended in miscarriage at 7 weeks due to aneuploidy. Thereafter, the patient underwent a second orthotopic transplantation and became pregnant. She delivered a healthy baby.

Andersen et al. reported a series of 6 women (some already reported in the paper by Schmidt et al.). Orthotopic autotransplantation was performed in all patients, 2 of whom received additional heterotopic transplants. They also observed restoration of ovarian function in all women within 20 weeks. Four of the six women conceived following assisted reproduction. One woman miscarried in gestational week 7 and another had a positive hCG test but no clinical pregnancy. Two others became pregnant after follicle puncture and ovum pick-up during natural cycles. Both delivered a healthy baby. These 2 women had undergone orthotopic transplantation of cryopreserved ovarian tissue according to the technique described by Donnez et al.

Is blocking ovarian function by GnRH agonist administration useful before chemotherapy?

The efficacy of GnRH analog treatment to protect gonads from the cytotoxic effects of cancer therapy is controversial. Previous studies have shown no difference in testicular failure rates after chemotherapy.
in male patients with or without GnRH agonist protection. Most prepubertal boys receiving chemotherapy and/or radiotherapy suffered azoospermia, even with GnRHa treatment. On the other hand, most animal and human studies have shown that GnRH agonists can protect primordial follicles during chemotherapy, but the majority of these studies are small, retrospective or non-randomized. The precise mechanism by which GnRH analogs protect primordial follicles from the effects of alkylating agents is still unknown. Possible mechanisms include 1) preventing follicular growth by suppressing gonadotropin secretion; 2) decreasing exposure to chemotherapeutic agents by reducing uterine-ovarian perfusion; 3) a direct effect of GnRHa on GnRH receptors, independent of the suppression of gonadotropin levels; 4) upregulation of intragonadal antiapoptotic molecules, such as sphingosine-1-phosphate. Although the results of published studies are encouraging, prospective randomized trials are required to confirm the protective effects of GnRHa treatment against the ootoxicity of chemotherapy. In fact, there are currently several large prospective randomized studies ongoing worldwide. Very recently, Ismail-Khan et al. presented the results of a prospective randomized clinical trial including 49 patients at the ASCO meeting. They concluded that GnRH agonists do not appear to benefit patients in preserving menstrual status. It should be borne in mind that GnRH analogs cannot protect primordial follicles from radiation therapy.

Ethical issues and safety

One of the most important ethical issues is to ensure that the intervention does not harm the patient by dangerously delaying cancer treatment and that no remnant cells are reintroduced by subsequent transplantation. On these points, we agree with Dudzinski who stated that policies to protect the patient’s future rights to her gametes, as well as those addressing the disposition of the gametes if the patient dies, need to be developed. Although an adolescent is more vulnerable when consent is sought in the rush to begin chemotherapy, she must be mature enough to understand the risks and benefits of the procedure. Consent must then be extensively discussed, with both the adolescent patient and her parents, in order to minimize the risk of conflict of interest or inadvertent caution. Respecting the code of good practice, all patients who may become infertile have the right to receive proper consideration of their interests for possible ovarian function preservation. The selection of cases should be carried out on the basis of a multidisciplinary staff discussion including oncologists, gynaecologists, biologists, psychologists and paediatricians. Counseling should be given and informed consent should be obtained from the patient. Cancer treatment takes priority over potential restoration of fertility, but offering the chance to preserve fertility may greatly enhance the quality of life of cancer survivors.

The transmission of lymphoma via grafts of ovarian tissue from diseased donor mice to healthy recipients was reported by Shaw et al. This study highlighted the risks of clinical transplantation of ovarian biopsy samples to women recovering from cancer, especially a blood-borne cancer. However, there are certain circumstances where the risk of cancerous involvement of the ovary is absent or minimal, and where autografting would present little or no danger. Screening methods must be developed to eliminate the risk of cancer cell transmission with reimplantation when there is a risk of cancerous involvement of the ovary, like in breast cancer or leukemia (Figure 5). In some diseases, other options must be considered, such as transplantation of isolated follicles, as recently described by Dolmans et al. In 2004, the Practice Committee of the ASRM summarized some important points to be taken into consideration, and Dudzinski underlined the need to develop policies to protect the patient’s right to self-determination with respect to her gametes and concluded that more research is required before adolescents can ethically be enrolled in clinical trials.

Figure 5. Breast cancer metastasis found in the ovary.
We do not fully agree with this conclusion. Indeed, approximately one third of young women exposed to chemotherapy develop ovarian failure. In 2008, we believe it is our ethical responsibility to propose cryopreservation of ovarian tissue to all adolescents and young women under IRB protocols having to undergo chemotherapy with alkylating agents. Indeed, is it ethical to simply accept the existing discrepancy between males and females with regard to their chances of preserving their fertility following cancer treatments? What do we then say to young women facing POF following chemotherapy, knowing that ovarian cryopreservation has been an option for more than 10 years? It will be too late to say “we should have done something”.

This is why, since 1996, we have systematically proposed cryopreservation prior to chemotherapy to all women under 35 years of age, when there is a risk of POF. So far, more than 300 ovarian cortex pieces have been cryopreserved and stored in our cryobank. We accept that ovarian tissue cryopreservation is a more innovative and invasive procedure than sperm cryopreservation and that all possible applications in adolescents are ethically complex. But we fully agree with Revel and Schenker who argued that ovarian cortex banking should be offered before chemotherapy in all cases where emergency IVF is not possible.

Key messages for clinical practice

1. The role of the oncologist in advising patients about fertility preservation options is to evaluate the risk of infertility of each specific cancer treatment in each individual patient. Fertility preservation options should be discussed and considered as soon as possible to maximize the chances of success.

2. The use of GnRH analogs in chemotherapy patients is controversial and should be further investigated. GnRH analogs are not indicated for patients undergoing radiation therapy.

3. Embryo cryopreservation should be considered as the first method of fertility preservation if the patient is pubertal, has a partner and is able to undergo a cycle of ovarian stimulation, which takes about 2 weeks.

4. For patients who need immediate chemotherapy and for young girls, cryopreservation of ovarian tissue is the only possible alternative and should be considered as an emergency procedure in order not to delay chemotherapy.

References


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