Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article | Published 1 October 2012, doi:10.4414/smw.2012.13645
Cite this as: Swiss Med Wkly. 2012;142:w13645

Fertility preservation in cancer patients

Review of the French speaking part of Switzerland and recommendations for different situations

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Summary

Due to constant progress in oncology, survival rates of patients (children and adults) with cancer are increasing. Consequently, the reproductive future of young cancer patients needs to be addressed carefully. Fertility preservation techniques are available and issues such as the time available for fertility treatments, patients' age, presence of a partner and patients' personal wishes have to be considered.

In Switzerland, a first therapeutic network (Réseau Romand de Cancer et Fertilité), was created in the French speaking part of Switzerland in 2006. Since 2010, a global Swiss network (FertiSave) has been created. The goal of these networks is to maximise the safety and efficacy of fertility preservation options offered to cancer patients without compromising their oncological prognosis. Patients' needs have to be identified, the therapeutic options evaluated rapidly and the optimal treatment promptly implemented in these urgent situations.

This article reviews the fertility preservation options currently available and makes recommendations for different specific cancer situations, consistent with the latest scientific evidence and in general agreement with international recommendations.

Key words: *cancer; fertility preservation; chemotherapy; radiotherapy; gonadotoxicity; premature ovarian failure; cryopreservation; ovarian transplantation; GnRH agonist; trachelectomy*

Introduction

In adult male cancer patients, sperm cryopreservation before cytotoxic treatment has been offered and efficaciously performed for several decades, even if it at times forgotten when caught in the stress caused by the diagnosis and the need for rapid initiation of treatment.

In women of reproductive age with cancer, there is also a need to discuss the consequences of their treatments on future fertility. The duration of amenorrhoe and risk of permanent failure greatly depend on the type of cancer and treatment (table 1, adapted from [1]), as well as the patient's age and specific susceptibility line. There is no direct comparison between women and men concerning the strength of effect of the different substances or regimen. However, the same classes of drugs seem to be equally toxic in men and women (i.e. alkylants).

The inherent complexity of this emerging field has required establishing a multidisciplinary approach, which guarantees a better and safer management than individual initiatives might offer. In Switzerland, the first multidisciplinary network of reproductive medicine specialists, gynaecologic/medical/paediatric oncologists, radiotherapists and psychologists ("Réseau Romand de Cancer et Fertilité, RRCF") was created in 2006 in the French Speaking part of the country (1.7 million inhabitants). The RRCF comprises the two University hospitals, but also regional public and private hospitals/infertility centres are invited to participate on a voluntary basis and to record their patients in the elaborated register. In practice, only patients of the two University hospitals and public hospitals have been recorded until now. The aims were to establish and coordinate fertility preserving measures tailored to the cancer type, personal characteristics and treatment envisioned [2]. Since inception, every counselling and fertility preservation measure offered by RRCF was codified in an elaborated register that documents the indication, diagnosis, planned oncologic treatment and fertility preservation

measure implemented or on the contrary, the patient's decline of such offers. To this date, 85 patients were handled in an emergency setting that offered a thorough evaluation and discussion conducted by a dedicated multidisciplinary task force with one or several consultations for discussing fertility preservation options with reproductive medicine specialists. From these 85 patients, 61% had a treatment (forty patients had controlled ovarian hyperstimulation with cryopreservation of gametes and/or pre-embryos and 12 patients had cryopreservation of ovarian tissue). A dedicated psychological counselling [3] has been routinely offered because of the stressful context: The shock caused by the diagnosis of cancer, the treatments envisaged, the fragility of life with the idea of possible death and, in the event of recovery, the risk of future infertility. All these concerns come together and need urgent decisions. The affected patients are not prepared and counselling is of paramount importance. The sources of stress that arise from cancer and fertility issues are multiple. First, Assisted Reproductive Technologies (ART) do not guarantee pregnancy after cancer. The patient is also not even certain of ever using the saved gametes or (pre-) embryos because fecundity may spontaneously occur, or she may elect not to conceive. Second, because ART is self paid in Switzerland as in many other countries, the costs of the emergency ART have to be assumed by the patient herself.

While other publications exist on fertility preservation networks [4], the present article's originality stands in the collective process of its undertaking that included all the parties at stake. Moreover, as other publications [4] schematised 3 oncologic situations only (breast cancer, borderline ovarian tumours and Hodgkin's Lymphoma, the present article includes larger arrays of oncologic pathologies (tumour types and clinical situations) in the discussion (i.e. different ovarian cancers, cervical cancer, endometrial cancer, leukaemia and paediatric oncologic situations).

The fertility preservation options are discussed, making practical recommendations in accordance with the latest scientific findings.

General remarks

All cancer patients of reproductive age (or younger) must be informed about fertility issues associated with their cancer and foreseen treatments. Fertility preservation is generally considered only in women under 40 years of age. Ovarian function is evaluated by a reproductive medicine specialist prior to fertility preservation measuring the antimullerian hormone (AMH) and antral follicle count (AFC). It is recommended to repeat AMH measurement one year after chemotherapy in order to assess the net follicular loss due to chemotherapy and to estimate ovarian function.

As certain chemotherapeutic agents may cause some cardiovascular complications, as for example adriamycin derivatives, follow-up of pregnancies is recommended in specialised centres.

Data on the risk of malformations or childhood malignancies in offspring of cancer survivors are however reassuring [5].

For better risk assessment and quality control, a register of all fertility preservation measures and techniques, including outcomes and complications, is of the outmost importance. The primary objective that should guide all fertility preservation counselling is to assure that any measure offered is not bound to harm by reducing the efficacy of cancer treatment. Moreover, the proposed options should not undermine the spontaneous pregnancy chances when these exist. In particular, any offer of fertility preservation measure that amounts to removing some gonadal tissue, as done for ovarian tissue cryopreservation, should be envisioned with due care and as little tissue as possible has to be cryopreserved. Generally speaking such measures should be avoided when natural pregnancy chances are real, as in the case of breast cancer, for the fear that the removal of gonadal tissue might harm natural pregnancy chances.

Techniques of fertility preservation

Sperm cryopreservation

Sperm can be cryopreserved in post pubertal men if spermatozoa are present in the ejaculate. Depending on several factors, artificial insemination, In-Vitro Fertilization (IVF) or Intracytoplasmatic Sperm Injection (ICSI) can be undertaken after recovery.

Cryopreservation of testicular tissue

When no spermatozoa are found in the ejaculate, testicular sperm extraction (TESE) and cryopreservation of testicular tissue can be offered, if the time frame (1 day) allows it. TESE-ICSI can be offered after recovery.

Table 1: Gonadotoxicity of chemotherapeutic agents.

High gonadotoxic potential	Moderate gonadotoxic potential	Mild or no gonadotoxic potential
Cyclophosphamide	Cisplatin with low cumulative dose	Bleomycin
Chlorambucil	Carboplatin with low cumulative dose	Actinomycin D
Melphalan	Adriamycin (Doxorubicin)	Vincristine
Busulphan	Etoposide	Methotrexate
Nitrogen Mustard		5-Fluoro-uracil
Procarbazine		Mercaptopurine
Dacarbazine		Treatment protocols for Hodgkin lymphoma without alkylating agents.
Ifosfamide		Prednisone
Thiotepa		Interpheron-alpha
Carmustine		
Lomustine		

ART with cryopreservation of unfertilised oocytes and/or (pre-) embryos

IVF/ICSI and cryopreservation of unfertilised oocytes and/or (pre-) embryos are offered worldwide. However, the Swiss Law for ART forbids the cryopreservation of cleaving stage embryos [6].

These techniques are applicable in post pubertal women. At least two weeks are required for implementing such measures before initiating the oncologic treatment. A hormonal stimulation of the ovaries is necessary for harvesting a maximum of oocytes, while avoiding the risk of ovarian hyperstimulation syndrome (OHSS). Several stimulation protocols exist. A special protocol for breast cancer (BC) has been developed that reduces estradiol levels within menstrual cycle limits, without compromising the oocyte crop [7, 8]. ICSI is generally applied in order to minimise the risk of fertilisation failure. If the patient has no partner or is unsure about her marital plans, it is better to cryopreserve unfertilised oocytes rather than (pre-) embryos. If the couple has already decided to start a family or has children together, (pre-) embryos (belonging to both partners,) are cryopreserved. In certain cases, a split option (with both oocytes and (pre-) embryos) is chosen.

Treatment costs have to be discussed with the patient, as IVF-ICSI is relatively expensive (Swiss Francs (CHF) 6,000–9,000) and not covered by the Swiss health insurance. After the cancer treatment, there can be additional costs (CHF 1,500–2,000 per cryocycle). Moreover, most centres have yearly fees for the cryopreservation (CHF 200–300 per year).

Risks, complications and success

Complications during or following IVF-ICSI treatments are very rare: oocyte pick-up (<1‰), OHSS (<1%), insufficient ovarian response (<5%).

Success depends on numerous factors. Pregnancy rates are higher with cryopreserved (pre-) embryos compared to unfertilised oocytes (implantation rate of one oocyte or (pre-) embryo being 10–15% or 6–8% [9], respectively).

Ovarian tissue cryopreservation (OTC)

This method consists in removal of ovarian tissue by laparoscopy or laparotomy. The amount of the ovarian tissue removed has varied according to the different practices with no consensus as of yet on the best measures. Generally, the amount depends on the expected ovarian damage.

There are theoretically two options of further utilisation after OTC:

1. Ortho-/heterotopic transplantation
2. In-vitro maturation (IVM) of primordial follicles (not yet accomplished in humans).

The main advantage of the second option is that there is no risk of re-introduction of cancer cells (no risk of recurrence), not excluded in the first option. The histological examination of a piece of ovarian tissue before freezing is always requested in order to exclude micro metastases. However, reports in the literature mention the risk of cancer recurrence after re-transplantation even in the case of negative histological examination [10].

Our recommendations concerning pre-existing conditions for OTC are depicted in table 2.

Very often, OTC is indicated in patients with breast cancer or lymphoma [11–14]. Orthotopic transplantation clearly outmatches heterotopic transplantation. So far, 18 births after re-transplantation have been reported worldwide [15]. As one spontaneous pregnancy/live birth has been reported after subcutaneous transplantation of ovarian tissue to a woman with a hormonal profile of complete ovarian insufficiency [16], it has yet to be proven that the reported babies were really conceived from the orthotopically transplanted and not from the residual ovarian tissue.

OTC and transplantation is still an experimental technique and many open questions remain, as the exact site of transplantation, the risks of relapse, etc. The success depends on the correct indication of OTC, the age of the patient, the technique of cryopreservation and the surgical technique of transplantation.

Agonists of Gonadotrophin Releasing Hormones (GnRHa)

After a transitory flare-up, GnRHa lead to gonadal suppression. The mechanism of action is that inhibition of the pituitary-gonadal axis inhibits temporally follicular development [17]. However, there is no clear evidence that GnRHa are efficient at preserving ovarian function after chemotherapy [18], as existing prospective randomised are inconclusive. There are even theories that GnRHa could be harmful during chemotherapy because GnRH receptors are expressed in up to 50% of ovarian and BC but not on primordial follicles [19, 20].

In two prospective randomised studies, GnRHa did not preserve gonadal function [21, 22]. However, two recent randomised studies on BC patients showed a benefit of GnRHa in ovarian protection [23, 24]. A meta-analysis, only including prospective randomised studies, showed an improved outcome after GnRHa [25]. Another meta-analysis, including 11 prospective studies (three randomised and eight non-randomised), showed also a better outcome after GnRHa [26]. However, a separate analysis of the three randomised studies did not show a protective effect of GnRHa any more [27]. Further randomised controlled studies are under way.

An important advantage of GnRHa is the prevention of uterine haemorrhage in the case of severe thrombocyt-

Table 2: Conditions that need to be fulfilled before cryopreservation of ovarian tissue.
Ovarian micro metastases are reasonably excluded by histological examination of samples.
Time frame of at least 3 days.
Health status of the patient allows anaesthesia and operation.
Planned cytotoxic therapy is known to induce a premature ovarian failure.
Age of the patient <35 years.
The chance of having a pregnancy with this ovarian tissue has to be weighed with the chance of having a spontaneous pregnancy after recovery.

openia induced by chemotherapy by inhibiting menstruations.

Transposition of the ovaries

This surgical technique consists of fixing the ovaries as far as possible out of the pelvis in case pelvic irradiation. By laparoscopy, the ovaries are mobilised, tagged with a clip and fixed cranio-laterally [28]. Ovulatory cycles can be achieved in up to 85% of patients below 40 years [29]. In post-pubertal women, radiation with 2 Gy leads to a loss of circa 50% of primordial follicles, and a loss of up to 100% is observed after 15 Gy [30]. Ovaries of pre-pubertal girls appear more resistant to damage from irradiation [31].

Risks include the common operative risks of a laparoscopy, chronic pelvic pain, often due to adhesions, which can mandate an operative revision or due to secondary necroses of the ovary or ovarial cysts [32].

Radical vaginal trachelectomy

Radical vaginal trachelectomy is an operative procedure preserving the uterus (see also chapter "Cervical cancer").

Combination of techniques

Methods of fertility preservation can be combined, i.e. cryopreservation of gametes/embryos with subsequent GnRHa.

If the combination of IVF-ICSI with sampling of ovarian tissue [33] can enhance pregnancy chances or if on the contrary it hampers spontaneous pregnancy by inducing premature ovarian failure has to be confirmed in further follow-up studies.

Recommendations of fertility preservation approaches in the various cancer cases

In all cases, an evaluation of the ovarian reserve should be conducted in order to assess the net benefit that can be expected from the foreseen fertility preservation measure. AMH levels and AFC scores indeed predict the ovarian yield that can be expected from COS [34]. From this will depend the number of harvested oocytes and in turn the calculated pregnancy chances to be expected from the measure.

Predicting natural pregnancy chances after chemotherapy only based on pre-chemotherapy AMH levels is probably impossible, as of now. However, it may be useful to estimate ovarian function after chemotherapy to have an idea on the chances of pregnancy without treatment [35, 36].

Breast cancer (BC)

Chemotherapy can interfere with ovarian function. But fortunately, especially with the combinations used in recent years, the chance of spontaneous ovarian function after chemotherapy for BC is relatively high in women under 40 years of age [37, 38].

In the classical therapeutic sequence – selected in most BC patients – surgery precedes adjuvant chemotherapy therapy. The recommended time interval between surgery and chemotherapy (3–6 weeks) normally suffices for conducting one cycle of COS without delaying the onset of chemotherapy. Conversely, when preoperative chemotherapy is preferred, COS is not advisable, as COS would have to be conducted while the tumour is still in place. In these cases OTC (or in vitro maturation) may be envisioned. However, OTC should be avoided if there is a significant chance of recovery of ovarian function / spontaneous pregnancy after chemotherapy.

In addition to oocyte/(pre-) embryo cryopreservation, GnRHa can be administered in ER-/PR-negative patients despite of a proven benefit (see above), preferably in the setting of a clinical trial.

Borderline ovarian tumour and ovarian cancer

Borderline ovarian tumour

Fortunately, 75% of cases are stage FIGO I with a long-term survival rate of nearly a 100%. In these cases, unilateral ovariectomy can be conducted and the uterus preserved. A surgical staging is recommended [39]. Afterwards, pregnancies can occur spontaneously, or ovarian stimulation can be safely used [40].

In advanced stages, conservative treatment can also be discussed, but the recurrence rate is high [41].

If a bilateral adnexectomy is required, preservation of the uterus has to be discussed. With this, oocyte donation later in life would still remain an option to fulfil the child wish.

Epithelial ovarian cancer

Patients with a stage FIGO IA, grade 1–2 have a 5-year survival rate of 90–95%. Also in these cases, it can be discussed performing unilateral ovariectomy (with a full surgical staging) and to preserve the uterus [39].

A regular follow-up is mandatory (clinical examination and Ca-125 every 3 months, ultrasound every 6 months, during 3 years). Surgery after completion of the child wish should be considered.

Non-epithelial ovarian cancer

The prognosis for these tumours is mostly good. In general, depending on the stage of the disease, they are cured after conservative surgery and adjuvant therapy.

Ovarian stimulation

In the nineties, there was a big fear that ovarian stimulation could enhance the risk of ovarian cancer [42]. Fortunately, these data have not been confirmed and newer data are quite reassuring [43, 44].

Cervical cancer

In FIGO stage IA1 and absence of lympho-vascular space invasion, conisation *in sano* may be sufficient, although standard therapy includes total hysterectomy.

In FIGO stage IA2 or IB1 with a tumour size of 2 cm or less (exceptionally until 3 cm) and negative regional lymph nodes, radical trachelectomy (ablation of the cervix and the parametria and conservation of the corpus uteri and the ovaries) with full pelvic lymph node dissection can be proposed.

Lympho-vascular space invasion is not a contraindication; however, the risk of recurrence is slightly increased. In all cases, a multidisciplinary evaluation (pathologist, gynaecologist, radiotherapist and oncologist) is warranted.

Before trachelectomy, the size of the lesion, the level of the cervical canal, and the distance between the superior pole of the lesion and the uterine isthmus have to be evaluated by Magnetic Resonance Imaging (MRI). In about 10% of the cases, lymph node or parametrical invasion is diagnosed only intra-operatively and trachelectomy has to be abandoned.

The oncologic results after trachelectomy are similar as compared to the traditional radical surgery (Wertheim); recurrence rates are around 5% in 5 years. In about 70%, pregnancies ensue after trachelectomy. However, late miscarriages and prematurity are increased after this procedure [45–48].

Endometrial cancer

General remarks

In all cases, the diagnosis of endometrial cancer must be revised by an experienced pathologist, for the fear that misdiagnosis is possible with dramatic consequences in young women.

MRI, with a sensitivity of 60–70% (experienced radiologist), is actually the best exam to evaluate myometrial invasion.

A laparoscopy can be undertaken in order to exclude an ovarian neoplasia, the risk of a synchronous ovarian tumour being 10–20% in this group of patients.

Because of the low risk of lymph node invasion in patients with FIGO IA G1-2 (approximately 2–3%), pelvic and/or para-aortic lymphadenectomy is generally not recommended.

Standard treatment for atypical hyperplasia is total hysterectomy. Early endometrial cancer treatment consists of hysterectomy and bilateral adnexectomy.

Conservative treatment in atypical hyperplasia and endometrial cancer

Only in cases of atypical hyperplasia and stages FIGO IA grade 1 (endometrioid type), a conservative management can be discussed. It comprises the application of systemic high dose progestins. Mean time of response varies between 4 to 8 months, requiring rigorous monitoring with biopsies every 3–4 months. There are no clear criteria to define the optimal duration of treatment [49]. Treatment has to be followed by hysteroscopy and histological examination of the endometrium before planning a pregnancy.

As soon as the desired family size is achieved, standard treatment is proposed.

Acute leukaemia

Healing rates of acute leukaemia vary between 75% (low risk) and 5–15% (high risk). Treatments usually require aggressive chemotherapy with a high systemic toxicity. Risk of amenorrhea and persistent infertility may be low after standard chemotherapy (<15%), but is very high if allotransplantation or total body irradiation (TBI) is administered (>90%) [50].

The major concern is the fact that acute leukaemia is a therapeutic emergency precluding the possibility of ovarian stimulation. Ovarian tissue transplantation is contraindicated because of the risk of re-implanting cancer cells [51, 10]. Thus, today, the possibilities of fertility preservation are unfortunately limited. However, should IVM of primordial follicles be technically possible in the future, OTC could perhaps be reconsidered.

Lymphoma

The risk of definitive infertility after a conventional first line treatment for Hodgkin or Non-Hodgkin Lymphoma is low. Fertility preservation is generally not indicated in the case of treatment with ABVD or R-CHOP [52, 53]. Ovarian tissue removal, especially if it is extensive, could even be contra-indicated in these cases because it could decrease the chances of spontaneous pregnancy after recovery.

Patients presenting high-risk Hodgkin Lymphoma and treated with a more intensive regimen like BEACOPP have a risk of long-term infertility of about 50% [54]. Fertility preservation methods should therefore be proposed. Additionally, some of these patients may also need radiotherapy of the pelvis; a pre-therapeutic oophoropexy may be indicated.

Special situations: relapses, allo/auto-transplantation

Patients presenting refractory or relapsed lymphoma are often candidates for salvage therapies, consisting of polychemotherapies with alkylating agents at high dosage, sometimes including TBI and frequently followed by autologous/allogenic stem cell transplantation. As the risk of infertility in these cases is very high (90%), fertility preservation methods should be discussed before starting salvage therapy.

GnRHa during chemotherapy

Studies have given contradictory results: GnRHa in combination with a BEACOPP regimen has been reported to be beneficial [55, 56], but these observations were not consistent in other trials [21, 22, 57]. Other prospective randomised studies are under way.

Paediatric Onco-Haematology

Due to the amelioration of oncologic treatments in the last 40 years, almost 80% of children who currently receive a diagnosis of cancer become long term survivors. Unfortunately, many treatments for childhood cancer are toxic for the gonads and 15% of the children will have a compromised reproductive function.

In the case of treatments with high infertility risks (high dose alkylating agents, TBI, bilateral ovarian surgery) fertility preservation has to be discussed with the multidisciplinary team [57, 59, 60]. A written informed consent (parents and possibly the child) is recommended.

Oncologic situations indicating discussion of fertility preservation are acute lymphoblastic and myeloblastic leukaemia, solid tumours and lymphomas (i.e. Wilms tumour, neuroblastoma, rhabdomyosarcoma, Hodgkin's disease).

In certain non-oncologic diseases (myelodysplastic syndromes, severe aplastic anaemia, primary immunodeficiency diseases and severe haemoglobinopathia), haematopoietic stem cell transplantation has also to be proposed. As this procedure requires conditioning regimen with highly gonadotoxic (alkylating) agents, fertility preservation has to be considered also in non-oncologic situations.

Pre-pubertal girls

OTC prior to sterilising treatments is the only option. After a multidisciplinary consensus, OTC should be discussed with the girl and her parents. While OTC is still experimental, research is very active in this field. It is important to keep in mind that while paediatric patients today will wish a pregnancy in 10 to 20 years or even more, many of the technical problems might actually be resolved by that time.

Post-pubertal girls

While cryopreservation of mature oocytes after ovarian stimulation could be offered in certain non-oncologic cases, this option is rarely possible in oncologic situations because chemotherapy has to be initiated immediately. OTC prior to cytotoxic treatment can be proposed. Ovarian protection during chemotherapy by GnRHa is still debated, but often proposed.

Pre-pubertal boys

As the production of spermatozoa begins at puberty, it is not possible to obtain sperm before the age of 12–13 years. The cryopreservation of immature testicular tissue is an experimental technique, only few laboratories in the world perform this approach and only in a research setting [61].

Post-pubertal boys

Sperm collection followed by cryopreservation is proposed.

Conclusion

Due to progresses in oncology, survival rates of cancer patients (children and adults) have been constantly improving. Hence, the reproductive future of these patients needs to be addressed carefully. Techniques of fertility preservation exist and must be discussed beforehand, taking into consideration the various cancer treatments, the time available, the general condition, the patients' ages and marital projects as well as their own personal wishes. Crucial to the good quality of the care provided is the establishment of a close functional collaboration between the primary oncology team and reproductive medicine specialists for always offering the best options possible.

Acknowledgements: We warmly thank Eleanore Hickey for her help in stylistic ameliorations of the English language.
Funding / potential competing interests: D. de Ziegler owns equity interest in Ultrast Inc., and sat on Advisory boards of Ferring Pharmaceuticals, Ibsen Pharmaceuticals and IBSA Pharmaceuticals. No financial support and no other potential conflict of interest relevant to this article was reported.

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