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ORIGINAL ARTICLE

State-of-the-art fertility preservation in children and adolescents undergoing haematopoietic stem cell transplantation: a report on the expert meeting of the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) in Baden, Austria, 29–30 September 2015

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Nowadays, allogeneic haematopoietic stem cell transplantation (allo-HSCT) is a well-established treatment procedure and often the only cure for many patients with malignant and non-malignant diseases. Decrease in short-term complications has substantially contributed to increased survival. Therefore long-term sequelae are reaching the focus of patient care. One of the most important risks of stem cell transplant survivors is infertility. As well as in the field of allo-HSCT also the field of reproductive medicine has achieved substantial advances to offer potential options for fertility preservation in both boys and girls. Access to these procedures as well as their financing differs significantly throughout Europe. As all European children and adolescents should have the same possibility, the Paediatric Diseases Working Party of the European Society for Blood and Marrow Transplantation organised an expert meeting in September 2015. This manuscript describes the recommendations for the diagnosis and pre-emptive procedures that should be offered to all children and adolescents in Europe who have to undergo an allo-HSCT.

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INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option for several malignant and non-malignant diseases. Continuous progress in the field has led to broader indications for HSCT, increasing the number of patients treated worldwide and leading to a better overall long-term

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outcome.[1] However, it is mandatory to consider long-term HSCT-related side effects, including fertility impairment, especially in the paediatric setting. The risk of infertility is high (>80%) in patients treated with TBI, high-dose cyclophosphamide, melphalan and busulfan.[2,3] The use of a reduced-intensity conditioning regimen is expected to decrease HSCT-related side effects, even though its impact on childhood and adolescent gonadal function and subsequent fertility has not been assessed. Although early studies seem to document a favourable evolution towards spontaneous puberty in children receiving any reduced-intensity conditioning, there are currently very limited data available on the long-term fertility for the same group of patients.[2,4,5] Reduced fertility can undermine the long-term quality of life in survivors and has been associated with depression and distress.[6] Finally, knowledge about the long-term effects after any type of conditioning regimen is generally lacking. The majority of the available data is from studies with a follow-up of <10 years. It is mandatory to have a specific pre-transplant consultation with the parents, and with the patients if appropriate, about the risks of infertility. Moreover, possible approaches to fertility preservation (FP) and future reproductive options, tailored to the patient's age, should be addressed in the same context.

Semen cryopreservation for post-pubertal male transplant recipients is routinely offered. Oocyte cryopreservation is an established and successfully implemented method for FP in women, and can be applied in post-pubertal girls in the HSCT setting. Procedures for prepubertal patients are under continuous development but are still considered experimental.[7] In June 2015, the first report was published of a live birth after re-implantation of autologous ovarian tissue cryopreserved from an almost 14-year-old premenarchal girl.[8]

In view of the rapid progress in FP techniques, the Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) gathered a panel of experts in transplantation and reproductive medicine to specifically address paediatric issues. A consensus conference with 33 physicians from 13 countries was held in September 2015. Divergent counselling practices throughout different countries, as well as differences in legal and cultural perspectives, exist and highlight the difficulties regarding this delicate issue.

In this consensus paper, the following key points will be addressed:

- Recommendations regarding pre-HSCT counselling about FP options in children and adolescents (state-of-the-art).
- Current programs, networks and practices in different European countries.
- Ethical issues.

PATIENTS AND METHODS

Counselling

Proper counselling is a difficult core task for physicians in the pre-HSCT phase. While having to honestly deliver hard facts and figures about HSCT-related risks, it is also necessary to honour the patient's autonomous wishes, ideas and individual judgements, to guarantee certified informed consent. The counselling has to respect ethical principles mainly derived from Kant: beneficence, autonomy and honesty. In the field of paediatric medicine, any type of counselling is more complex than in adults because the relationship is not dual but triangular due to the need to include the parents.

Patients and parents have to be informed about the indications for transplantation, transplant procedures, acute side effects of the procedure and the expected long-term outcomes. Mentioning possible long-term side effects, including fertility issues, often increases concerns about the procedure, even though the procedure suggests long-term survival after HSCT.

Of all the information that the parents receive during the pre-transplant interview, the risk of infertility appears to be the most devastating news. Psychologists and psychiatrists explain this risk as a disruption of life continuation because there will not be a next generation. Therefore, physicians have to offer various possibilities for FP that are adjusted to the individual patient characteristics and available medical resources. It is also extremely important to be very clear about the standard and experimental options for FP. A multidisciplinary counselling session is mandatory and should optimally include a haemato-oncologist, a fertility specialist, and if possible, a psychologist.

During the disease course, whether the patient has a severe non-malignant disease or haematological malignancy, the parents and patients are required to follow medical advice with substantial restrictions on their individual autonomy. In this setting, a discussion about the different options available for FP offers the families an opportunity to participate in the decision-making process. The prerequisite is a clear and complete picture of the various options. Fertility and sexuality have to be explained and differentiated. Being infertile is not equal to the absence of a satisfying sexual life. Moreover, it is important to consider that most of the patients will have to go through puberty in a completely different way than their contemporaries. Handling the feelings that their body has betrayed them, in addition to dealing with the changes that occur during puberty are important burdens/conflicts that often lead to a lack of self-esteem and dissociation of the body and soul. That is why this subject should be included in the follow-up after surviving the disease because these young patients have to reorient with their surroundings after having gone through a life-threatening experience.

Concepts of fertility, child bearing and parenthood are strongly influenced by culture. Therefore, an individual's opinions regarding semen preservation, masturbation or electroejaculation to obtain semen, as well as ovarian or testis biopsies, may strongly differ depending on the ethnic and cultural background. These aspects have to be considered during the counselling.

In the interest of the child, the PDWP recommends that counselling related to FP opportunities should be offered to each patient receiving stem cell transplantation (SCT), as part of the pre-SCT workup by a dedicated and trained team including a transplant physician as well as a fertility FP specialist. The presence of a dedicated nurse and a psychologist during the counselling is strongly recommended to create a broader communication opportunity for the patient, who may be more at ease with non-medical staff.

The counselling should including the following information:

(1) Infertility risk assessment considering the patient's underlying disease, age, pre-SCT treatment, the planned conditioning regimen and known co-morbidities that may impact fertility regardless of SCT.
(2) Overview of established and experimental FP techniques tailored to the patient's sex, age and underlying disease.
(3) In-depth discussion with the patient and his/her family about the best applicable FP strategies to meet his/her specific needs, and a discussion of the risk of side effects associated with the procedure itself.

Methods and options for fertility preservation in girls

Several options exist to preserve ovarian steroid secretion and fertility during gonadotoxic treatment for malignant or non-malignant disease. The aim of these methods is to either shelter the ovary from the toxic effects of chemo- or radiation therapy by co-administering gonadotropin-releasing hormone agonists (GnRH-a) and shielding the ovaries from potential ovarian irradiation, or by storing the gametes for future use by cryopreserving fertilised eggs (embryos), unfertilised egg or ovarian tissue.

Cryopreservation of ovarian tissue. Cryopreservation of ovarian tissue for potential later maturation and gamete production is the only option for FP for prepubertal girls, as these girls cannot undergo the ovarian stimulation and aspiration that is available to post-pubertal girls or women due to their young age.[9] It appears to be safe to schedule cryopreservation surgery at least 1–2 weeks before beginning a conditioning regimen and transplant procedure. An ovary or parts of an ovary have to be removed surgically, often by laparoscopy. This surgery may be performed during the same anaesthesia needed for an other procedure as central line insertion.

At a later time point when there is a desire for pregnancy and no 'natural conception' is possible due to ovarian failure, the tissue can be re-transplanted into females who were treated for non-malignant disease. The potential risk of re-implanting malignant cells in females who received a transplant for malignant disease is still being debated.

Some successful births have been reported after cryopreservation and transplantation of ovarian tissue.[10] However, there have not been any published reports of either pregnancy or live birth in a patient who underwent ovarian tissue cryopreservation before puberty. Of note, a live birth after cryopreservation of ovarian tissue performed during puberty, but before menarche, was recently reported.[8] Theoretically, the chances of becoming pregnant are greater in patients with a higher ovarian backup and follicle density in the cryopreserved and transplanted tissue.

The question of how much tissue should be removed in view of the cryopreservation of ovarian tissue is still controversial. Certain clinicians advocate the removal of one entire ovary,[11–13] whereas others advocate the removal of half of one ovary or parts of both ovaries.[6,11] The important issue is to store enough tissue to maximise the chances for ovarian recovery after autologous ovarian transplantation while still allowing for spontaneous recovery of the ovarian function with the tissue remaining *in situ*. Whether to remove the tissue by laparoscopy or laparotomy also varies between the clinicians, although it seems that most centres prefer laparoscopy if possible.[11–14] No serious complications of the collection of ovarian tissue for cryopreservation have been reported in the literature.[6] Different possibilities exist regarding the later re-transplantation of the ovarian tissue. The cryopreserved tissue can be re-transplanted by laparoscopy or laparotomy into the pelvic peritoneum, into the ovary or on the ovary. It is unclear which method provides the highest pregnancy rate, and it remains unclear how much cryopreserved tissue should be transplanted. It is advisable to check the tubal patency during the procedure. Heterotopic re-implantation (in the underarm, for example) is also possible.

As described above, only one report of a successful delivery of a healthy infant has been reported after autologous transplantation of ovarian tissue in an adult woman, who had her tissue stored during puberty,[8] but the success of the procedure has been documented in adult women who received their own ovarian tissue cryopreserved after puberty and menarche, with the delivery of more than 60 babies worldwide.[10,14,15]

In the case of disseminated diseases such as leukaemia, ovarian tissue may contain malignant cells. In these patients, the tissue cannot be transplanted. One possible option is *in vitro* maturation, but this procedure remains experimental and no births have been reported to date.[16–18]

Finally, because the quantity of cryopreserved tissue is small and follicles partially degenerate during cryopreservation, thawing and transplantation, the grafts are expected to be active for only a few years. Therefore, a transplant should only be intended to restore fertility, although cases of puberty induction have been reported[19,20]

Gonadal shielding. In girls undergoing TBI, shielding the ovaries can be considered, although this procedure has only been described in a few case reports. In patients with leukaemia, this procedure would raise concerns regarding residual leukaemic cells, which may increase the risk of relapse.[21]

Hormonal stimulation. Ovarian stimulation and subsequent oocyte collection with the aim of cryopreserving unfertilised oocytes or embryos fertilised with donor sperm can be an alternative method of FP in post-pubertal girls. Before egg retrieval is possible, the ovaries must be stimulated with gonadotrophins, which can be administered at any point in the cycle according to the most recent published results, and this procedure requires a stimulation time of up to 2 weeks. Depending on the age and ovarian reserve, an average of 10–13 oocytes can be obtained per treatment cycle.[22] The use of a vaginal probe when performing the ultrasound and oocyte aspiration can be traumatic and uncomfortable in post-pubertal girls who have not engaged in sexual activity.[1,23]

Hymen integrity is not an absolute contraindication *per se*, but cultural issues may hamper this procedure, despite the possibility of surgical reconstruction. However, case reports exist describing positive results in selected cases.[24] This method is much more common and probably offers much better chances of fertility as compared to ovarian tissue cryopreservation. However, a longer amount of time is needed to collect a sufficient number of oocytes.

In addition, stimulation may induce hyperstimulation syndrome. This risk has to be considered.

To increase the success rate during highly gonadotoxic therapies, ovarian stimulation may be combined with cryopreservation of ovarian tissue.[25,26] The stimulation can be started within 2 days after laparoscopy. This method, as well as double ovarian stimulation, has not been fully established; however, this method has already been reported.[25] The time frame needed for the full treatment is ~2–3 weeks.

GnRH-a. Finally, co-treatment with a GnRH-a during the course of chemotherapy has been suggested as a way to protect the ovaries of adult women against the detrimental effects of chemotherapy, possibly by inducing a hypo-oestrogenic state, which causes a reduction in the utero-ovarian perfusion resulting in a decreased total cumulative exposure of the ovaries to the chemotherapeutic insult.[1] However, using a GnRH-a in prepubertal girls is not reasonable because the ovaries are already in a hypogonadotropic state.

Methods and options for fertility preservation in boys

Semen cryopreservation. Cryopreservation of semen is the easiest, safest and most accessible way to safeguard fertility in adult and adolescent male patients facing HSCT. All boys with scheduled HSCT should be examined regarding their pubertal development (Tanner stage and testicular volume). If the boy is older than 12 years or the testes are 6–7 mL (that is, Tanner stage 3, whatever the age), there is a reasonable probability to find sperm in the ejaculate.[7,27] However, it must be emphasized that no clinical parameter can accurately predict the presence of sperm. Semen cryopreservation should be offered to all boys who are mature enough to produce sperm. If a pubertal boy is unable to produce an ejaculate, alternative methods such as vibrator stimulation or electrostimulation during anaesthesia can be offered. A testicular biopsy to collect intra-testicular sperm is an alternative.[27] Semen cryopreservation cannot be performed in a boy who has already started chemotherapy. Therefore, boys should always be offered sperm cryopreservation at the time of the initial diagnosis of malignancy, even when HSCT is not included in the first-line therapy. However, the boys should know that even if they are able to produce a semen sample, the quality may be insufficient for cryopreservation. Some diseases, such as Hodgkin's disease, may be associated with azoospermia at the initial diagnosis.

Hormonal suppression and gonadal shielding. Gonadal protection by means of hormonal suppression is based on the principle that suppression of gametogenesis renders the gonads less sensitive to the effects of cytotoxic drugs and irradiation.[28] Unfortunately, attempts to develop a successful gonadal protection strategy have failed in humans and non-human primate models.[28] The protective effects of shielding or removing testes from a radiation field are well known. All efforts should be made to minimise the radiation exposure of the testes, such as optimal dose planning and careful selection of the irradiation modality, as well as shielding. Again, in the leukaemia setting, any shielding would raise concerns regarding the possibility of residual leukaemic cells in the testes, which would increase the risk of relapse.

For prepubertal boys, there are no established FP options that can be offered at present.[29] In these boys, cryopreservation of a testicular biopsy can be considered. The tissue should be cryopreserved with a protocol optimised for preserving immature germ cells.[7] Theoretically, the testicular spermatogonia can later be differentiated into mature sperm. This approach is still experimental and no pregnancies have been reported. Patients who are peripubertal but are unable to produce a suitable semen sample may also proceed to testicular biopsy for intra-operative extraction. In patients with sperm present, the tissue can be split into two portions for storage. One can be cryopreserved using the immature testis preservation protocol, whereas the second portion can be stored using a protocol aimed at the collection and storage of mature sperm.[7]

Although autologous transplantation of cryopreserved testicular tissue or cells may represent a future approach to preserve male fertility, contamination of the testes with malignant cells may prevent their subsequent re-implantation in patients with diseases such as leukaemia. In the future, *in vitro* germ cell maturation, if feasible, would provide the best strategy to overcome the risk of contamination. Three-dimensional and organ culture systems offer the possibility of differentiating immature male germ cells up to the stage of elongated spermatids, a procedure that is still experimental.[30]

In summary, in post-pubertal girls, if enough time is available (that is, in patients receiving a transplant for a non-malignant disease other than sickle cell anaemia), oocyte cryopreservation after hormonal stimulation remains the most successful treatment to date. If this approach is not possible, cryopreservation of ovarian tissue can be performed. In peri- and post-pubertal boys, cryopreservation of sperm is an option that can already be offered. For both prepubertal boys and girls, cryopreservation of gonadal tissue can be offered, but has so far not led to any pregnancies. The risk of contamination of the cryopreserved gonadal tissue with malignant cells is a contraindication for re-implantation, and only experimental approaches are available in this situation.

RESULTS

Current practices/networks

FP is currently being considered and discussed in the European SCT centres who contributed to this consensus paper. However, there are considerable variations throughout the centres. The FP procedure(s) offered to each patient referred for SCT varies according to national recommendations, local logistics, technical experience, financial considerations and the awareness of the FP possibilities among the patients, their families and the medical staff.

A few established national or multinational recommendations exist. In France and Israel, they compose part of the national law, whereas in other countries, there may be either national or local recommendations. Some of these practices are described below:

In France, all patients at risk of loss of fertility due to treatment are, since 2004, guaranteed counselling for FP by law.[31] This law states that 'Any person whose medical care is likely to impair fertility or whose fertility may be impaired prematurely can benefit from the collection and preservation of (his/her) gametes or (his/her) germinal tissue, to achieve, to (his/her) benefit, medical assistance for procreation, or for the preservation and restoration of fertility. The collection and preservation are subordinate to patient or to parent or legal guardian consent.'

In Israel, ovarian cryopreservation is included in the national health regulations. Patients who are candidates for SCT are referred for FP counselling and further gonadal tissue preservation. Cryopreservation of the ovarian cortex is indicated in cases where a highly gonadotoxic anti-neoplastic regimen will be administered. For prepubertal boys who are candidates for highly gonadotoxic protocols, an experimental procedure of testicular cryopreservation is available at two medical centres.

In the Nordic countries, a formalised consensus or cooperation exists for male FP. In 2013, the 'Nordic Centre for Fertility Preservation' was established to combine prepubertal testicular biopsies for FP into a common project and quality control procedure. Presently, Sweden, Finland and Iceland are performing studies under a cooperative protocol, with centralised quality analysis and in consensus with ethical licences. The FP programmes in these countries are financed by the national insurance systems. A common set of recommendations was provided in 2012 within the multidisciplinary Nordic network and Nordic Society of Paediatric Haematology and Oncology (NOPHO), recommending that all males and females must be offered proper counselling and the possibility of FP if a risk of fertility injury due to oncological treatment, including SCT, exists. Similar national recommendations exist in the Netherlands. In other countries, recommendations exist for the local treatment centres, which are often based on local experience and technical possibilities.

Denmark has a long tradition of awareness of reproductive damage following cancer treatment in childhood,[32] and an example of the Danish logistic is provided below:

Cryopreservation of semen has been offered to post-pubertal boys since the 1990's, and cryopreservation of ovaries for pre- and post-pubertal girls has been offered since 2000, if the patient was referred for SCT. Since 2014, cryopreservation of testicular tissue from prepubertal boys has also been an option. No re-implantation has been performed in this cohort to date. All costs for counselling, laparoscopic surgery and tissue storage in nitrogen freezers are covered by the national health insurance. When the child or young adult is accepted for SCT, the referring centre is encouraged in the acceptance letter to secure relevant FP. Cryopreservation of semen in post-pubertal boys with non-malignant disease is performed, if possible, during the screening procedure, ~3 weeks prior to SCT. In post-pubertal boys with malignant disease, semen is obtained at the initial diagnosis or relapse, before the initiation of chemotherapy. In prepubertal boys, testicular tissue is accessible for cryopreservation pre-SCT; however, this procedure has only been performed in boys with non-malignant disease to date. In girls, surgery to obtain ovarian tissue is ideally performed more than 3 weeks prior to conditioning therapy, regardless of the diagnosis. Ovarian cryopreservation is performed in girls with acute leukaemia only if the patient is in good clinical condition, not severely neutropenic and in full remission. The surgical removal of gonadal tissue is performed at the referring centre, whereas the cryopreservation procedure is centralised in Copenhagen. Re-implantation of

Table 1. The currently available routine and experimental techniques for fertility preservation in girls

	Prepubertal	*Pubertal*
Established	• Gonadal shielding – Irradiation of the pelvis – Excluded: patients with TBI • Transposition of ovaries – Irradiation of the pelvis	• Gonadal shielding – Irradiation of the pelvis – Excluded: patients with TBI • Transposition of ovaries – Irradiation of the pelvis • Hormonal stimulation for oocytes cryopreservation • GnRH-a (controversial)
Experimental	• Cryopreservation of ovarian tissue	• Cryopreservation of ovarian tissue

Abbreviation: GnRH-a = gonadotropin-releasing hormone agonists.

Table 2. The currently available routine and experimental techniques for fertility preservation in boys

	Prepubertal	*Pubertal*
Established	• Gonadal shielding – Irradiation of the pelvis – Excluded: patients with TBI	• Gonadal shielding – Irradiation of the pelvis – Excluded: patients with TBI • Sperm cryopreservation – After ejaculation, vibrator stimulation or electrostimulation under anaesthesia • Testicular biopsy for sperm extraction
Experimental	• Testicular biopsy for spermatogonial stem cell cryopreservation	

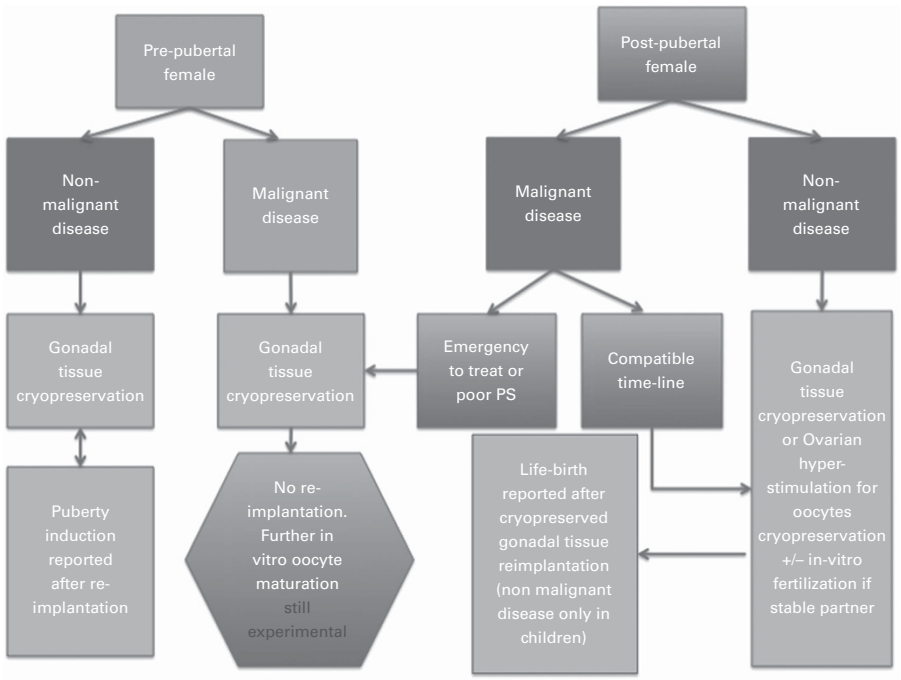

Figure 1. The proposed algorithm for fertility preservation in girls. A full colour version of this figure is available at the *Bone Marrow Transplantation* journal online.

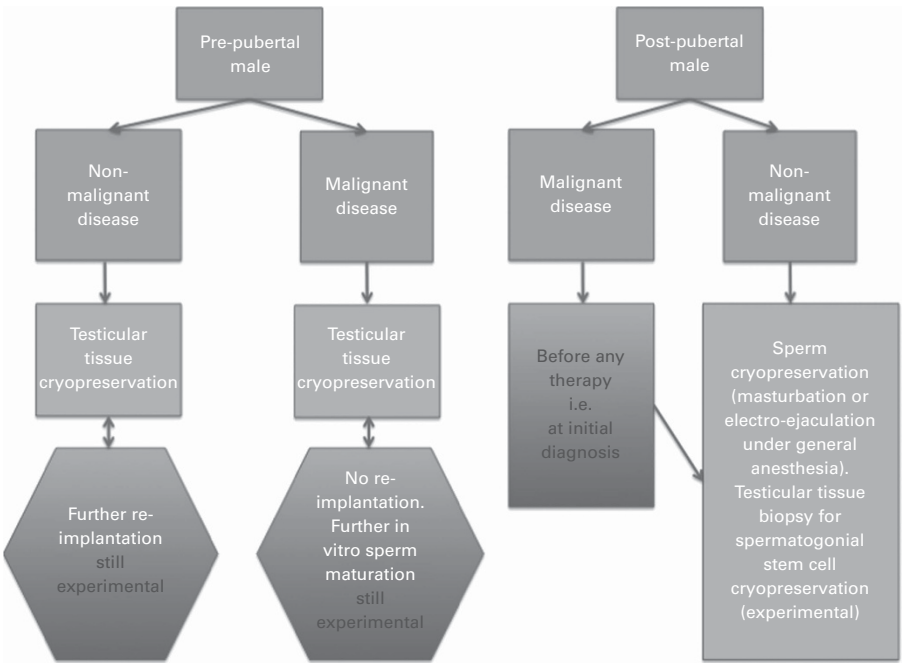

Figure 2. The proposed algorithm for fertility preservation in boys. A full colour version of this figure is available at the *Bone Marrow Transplantation* journal online.

ovaries is offered to women with proven infertility for all diagnoses except acute leukaemia. All transplanted children are followed by paediatric endocrinologists throughout puberty, allowing for optimal puberty induction, followed by age-adjusted fertility counselling.

Implementation/timing of the current practice

With the present recommendations, the PDWP of the EBMT has the primary aim of safeguarding the right to FP counselling for each paediatric patient undergoing SCT. The need to have joint recommendations on FP counselling derives from the evidence that different countries currently have a wide variety of approaches to this topic, which reflects local differences in the technical and economical availability/sustainability of different FP techniques, as well as the experimental nature of some of these techniques (Tables 1 and 2). The current recommendations consider the fact that SCT recipients have to implement FP in a complex medical and psychological peri-SCT setting, sometimes within a limited time frame.

Considering the above-mentioned challenges associated with FP in paediatric SCT recipients, it is a specific aim of these recommendations to raise awareness about the rights of each child to receive balanced and tailored counselling in his/her best interest for FP, accounting for his/her age-related understanding of infertility issues, and his/her physical and psychological commitment to undergo FP-related procedures.

The FP task force should implement a basic framework of guidelines to guarantee timely and efficacious counselling for each patient approaching SCT that can be adjusted to the circumstances and capabilities of each individual centre.

The critical points to be considered in this regard include:

(1) Adequate time for the patient and the family to understand and decide about possible FP-related interventions.
(2) The available pre-SCT time frame to proceed to possible FP procedures considering possible haematological risk factors in cases where surgery is required or when a planned procedure that will be performed under general anaesthesia may be suitably used for multiple interventions if required.
(3) Logistical coordination between different medical and laboratory teams, possibly within different medical specialties.

Considering the complexity and multidisciplinary nature of FP techniques, the PDWP recommends that the FP task force at each centre should be responsible for:

(1) Regularly updating the spectrum of locally available FP-related standard and experimental procedures.
(2) Identifying dedicated teams and centres available locally for FP procedures and liaise with them to create a network that can support the patient.
(3) Identifying economic support/constraints that may limit the availability of different techniques in different centres and that should be clarified with the families.
(4) Working with the identified FP teams and centres to implement and constantly improve the available FP practice in the local area.

FP is a rapidly evolving field in paediatrics, the EBMT PDWP therefore recommends that education and frequent updates on this subject become part of the standard continuing education offered for SCT-related medical and nursing staff at each centre.

Moreover, the EBMT PDWP suggests that a broader FP policy should be implemented among the different centres to prompt further awareness in the collection of long-term data on the fertility/endocrine follow-up for each patient transplanted in childhood or adolescence. Indeed, the long-term monitoring of patients' outcomes is the only quantifiable end point that will tell the paediatric community about its progress in safeguarding the patient's right to his/her FP.

DISCUSSION

Summary and implications

During the past few decades, tremendous progress has been made in avoiding complications after allogeneic SCT (allo-SCT) and also in improving the relapse-free survival. This progress has been achieved by sophisticated donor selection, optimising the treatment of GvHD, advancing antiviral prophylaxis and treatment, and improving the surveillance for remission in patients with malignant disease, potentially followed by pre-emptive immunotherapy to avoid frank relapse.

These advances have not only led to improved survival rates in children and adolescents in need of allo-SCT, but have also made it possible to offer this type of treatment to an increasing number of patients for whom allo-SCT is currently the only potential curative treatment option (for example, for patients with thalassaemia and sickle cell disease, as well as many other inborn errors). As a consequence of this development, not only short-term complications but also long-term sequelae, must now be considered. One of these long-term complications is the potential loss of fertility in children and adolescents undergoing allo-SCT.

On the other hand, especially in the field of reproduction medicine, impressive advances have also been achieved to offer potential options for FP in both girls and boys, pre- and post-puberty, as described in detail in this report. As access to treatment options for FP, as well as their financing, differs significantly throughout Europe the EBMT PDWP organised this expert meeting to elaborate on the accessibility and funding practices for FP treatments for European children and adolescents. The EBMT PDWP has established recommendations for the diagnosis and pre-emptive procedures that should be offered to all children and adolescents in Europe who have to undergo life-saving allogeneic SCT (Figures 1 and 2). This expert meeting describes the current possibilities regarding FP options to support state-of-the-art treatment for all junior patients in Europe and to provide enough scientific evidence for financing these procedures by the health-care systems in Europe.

Finally, as gonadal tissue injury begins with the first course of chemotherapy, it appears to be important to establish a strong discussion and collaboration with the non-transplant paediatric oncologists in the future; however, there have been no strong data defining the best schedule to apply FP during a patient's history to discriminate detrimental and useless procedures from mandatory FP techniques.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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