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Clinical guide to fertility preservation in hematopoietic cell transplant recipients

S Joshi[1,21], **BN Savani**[2,21], **EJ Chow**[3], **MH Gilleece**[4], **J Halter**[5], **DA Jacobsohn**[6], **J Pidala**[7], **GP Quinn**[8], **J-Y Cahn**[9], **AA Jakubowski**[10], **NR Kamani**[11], **HM Lazarus**[12], **JD Rizzo**[13], **HC Schouten**[14], **G Socie**[15], **P Stratton**[16], **ML Sorror**[3], **AB Warwick**[17], **JR Wingard**[18], **AW Loren**[19], and **NS Majhail**[20]

NS Majhail: nmajhail@nmdp.org

[1]Nationwide Children's Hospital, Columbus, OH, USA [2]Vanderbilt University Medical Center, Nashville, TN, USA [3]Fred Hutchinson Cancer Research Center, Seattle, WA, USA [4]Department of Haematology, St. James's University Hospital, Leeds, UK [5]Division of Hematology, University Hospital Basel, Basel, Switzerland [6]Division of Blood and Marrow Transplantation, Children's National Medical Center, Washington, DC, USA [7]Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL, USA [8]Department of Health Outcomes and Behavior, Moffitt Cancer Center, Tampa, FL, USA [9]Department of Hematology, University Hospital, Grenoble, France [10]Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA [11]Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC, USA [12]Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH, USA [13]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA [14]University Hospital Maastricht, Maastricht, The Netherlands [15]Hopital Saint Louis, Paris, France [16]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, USA [17]Department of Pediatrics, Uniformed Services University, Bethesda, MD, USA [18]Bone Marrow Transplant, Shands HealthCare, University of Florida, Gainesville, FL, USA [19]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA [20]Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, Minneapolis, MN, USA

Abstract

With broadening indications, more options for hematopoietic cell transplantation (HCT) and improvement in survival, the number of long-term HCT survivors is expected to increase steadily.

Correspondence: Dr NS Majhail, Center for International Blood and Marrow Transplant Research, National Marrow Donor Program, 3001 Broadway St NE, Suite 100, Minneapolis, MN 55413, USA.
[21]S Joshi and BN Savani are co-first authors in this study.

CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

NSM had full access to all of the data in the study and had final responsibility for the integrity of the data, the accuracy of the data analysis and the responsibility for the decision to submit for publication. The concept for this review was prepared by SJ, BNS, EJC, MHG, JH, DAJ, JP, GPQ, AWL and NSM. All authors contributed to the preparation and writing of this review and critically revised the manuscript. All authors have reviewed and approved the final version of the manuscript.

Infertility is a frequent problem that long-term HCT survivors and their partners face and it can negatively impact on the quality of life. The most optimal time to address fertility issues is before the onset of therapy for the underlying disease; however, fertility preservation should also be addressed before HCT in all children and patients of reproductive age, with referral to a reproductive specialist for patients interested in fertility preservation. *In vitro* fertilization (IVF) and embryo cryopreservation, oocyte cryopreservation and ovarian tissue banking are acceptable methods for fertility preservation in adult women/pubertal females. Sperm banking is the preferred method for adult men/pubertal males. Frequent barriers to fertility preservation in HCT recipients may include the perception of lack of time to preserve fertility given an urgency to move ahead with transplant, lack of patient–physician discussion because of several factors (for example, time constraints, lack of knowledge), inadequate access to reproductive specialists, and costs and lack of insurance coverage for fertility preservation. There is a need to raise awareness in the medical community about fertility preservation in HCT recipients.

Keywords

hematopoietic cell transplantation; autologous; allogeneic; fertility preservation; pregnancy; assisted reproduction

INTRODUCTION

Infertility occurs frequently in long-term survivors of hematopoietic cell transplantation (HCT).[1–4] Young HCT survivors frequently report infertility concerns as a late effect of HCT and loss of fertility can have a negative impact on their reproductive and overall quality of life.[3,5–7] Indeed, there is evidence that HCT survivors have continued concerns about their fertility even 10 years after treatment.[3]

For HCT recipients interested in preserving fertility, important considerations include the contribution of pre-transplant chemotherapy and radiation therapy exposures to infertility, the urgency to move ahead with transplantation given the high-risk nature of underlying disease, and physician and patient barriers to discussing fertility. The Center for International Blood and Marrow Transplant Research (CIBMTR) recently conducted a survey of HCT physicians to understand their practices and perceptions regarding fertility preservation.[1] Lack of information and educational materials for health-care providers specific to fertility issues in HCT recipients was identified as an important barrier to facilitating physician–patient discussion on fertility preservation.

To address this need, the CIBMTR Late Effects Working Committee assembled a task force to provide guidance on fertility preservation for transplant and non-transplant providers who care for HCT recipients. The American Society of Clinical Oncology has recently updated its guidelines for fertility preservation in cancer patients.[8] The American Society of Clinical Oncology guidelines are applicable for most HCT recipients. In addition, this review presents options for fertility preservation that are specific for HCT recipients. Recommendations are based on best available evidence, and where evidence was lacking, consensus opinion of the task force members is given. Recommendations apply to recipients of autologous and allogeneic HCT.

MECHANISM, DIAGNOSIS AND PATTERNS OF GONADAL FUNCTION RECOVERY IN HCT RECIPIENTS

Ovarian failure after HCT

Oocyte numbers, approximately two million in the female fetus, start to decline shortly before birth.[9,10] This age-dependent pool of follicles, or ovarian reserve, is a determinant of the relative impact of cytotoxic therapy on fertility.[11] Granulosa cells that support oocytes within developing follicles are exquisitely sensitive to radiation, especially during the early and intermediate stages of follicular development.[11–13] During late follicular development, granulosa cells are no longer dividing and thus are more radio-resistant. At doses of radiotherapy or chemotherapy insufficient to induce immediate acute ovarian failure, there may be a reduction in ovarian reserve rather than outright acute ovarian failure.[14] Survival of primordial follicles may also preserve some ovarian reserve. Reduced ovarian reserve may manifest later as premature menopause.[15]

Indicators of ovarian failure—There are several clinical and laboratory indicators of gonadal failure in women. Clinical indicators include failure to go through puberty, absent menstruation (primary or secondary) and menopausal symptoms. Laboratory indicators include elevated serum follicle-stimulating hormone and luteinizing hormone levels coupled with low estradiol levels, a low level of anti-mullerian hormone and reduced numbers of antral follicles on ultrasound.[16–18] Two follicle-stimulating hormone levels in the menopausal range measured at least 1 month apart are frequently associated with amenorrhea/oligomenorrhea and low estradiol levels are strongly suggestive of ovarian failure.[16,17] Normal clinical and laboratory parameters do not confirm fertility, however, and the only definitive way of demonstrating fertility is pregnancy.

Effect of HCT on ovarian function—Ovarian failure after HCT has been observed in 65–84% of transplant recipients.[2,19,20] However, it is important to recognize that studies assessing fertility after HCT are limited by the fact that they have not accounted for whether patients were actually trying to conceive. Exposure to high-dose CY, BU or TBI is associated with gonadal failure, whereas younger age at transplant (<30 years) is associated with a lower risk of ovarian failure.[21–23] One of the most comprehensive studies of pregnancy in pediatric and adult HCT survivors reported that 32 of 708 (4.5%) of post-pubertal females became pregnant after HCT.[19] Pregnancies were most likely to be reported in patients who had been exposed to CY only conditioning regimens, compared with BU-CY or TBI. Even where gonadal recovery and pregnancy occur, it is important that the patient be aware that their ovarian reserve may be reduced by conditioning or pre-HCT chemo-radiotherapy and that premature menopause remains probable.

Testicular failure after HCT

Germ cells in the testes normally continue to produce sperm during adulthood. Gonadotoxic therapies adversely affect the germinal epithelium, possibly leading to azospermia or oligospermia.[24,25] The risk of gonadal failure is dependent on the type and intensity of therapy and high-dose conditioning regimens may be associated with azoospermia rates

exceeding 90%.[24] Azoospermia is less frequent in patients conditioned with BU and CY (50%) and uncommon in those treated with CY alone (10%).[26]

TBI has been shown to have a central role in infertility in men.[26–28] It is possible that the strong impact of TBI on infertility masks other potential risk factors. Data examining the relationship between sperm recovery and GVHD are scarce.[27–30] An European Group for Blood and Marrow Transplantation study has reported chronic GVHD as an important adverse risk factor for sperm recovery in patients not conditioned with TBI. Independent of TBI exposure, age greater than 25–30 years at HCT can also contribute to infertility.[27–29] Interestingly, abnormal semen characteristics (oligospermia, azoospermia, sperm motility problems) have been described in 25–50% of male cancer patients even before any form of gonadotoxic therapy.[31–33]

Indicators and pattern of testicular failure—Leydig cells are less vulnerable to chemotherapy and radiotherapy than Sertoli and germ cells; typically serum luteinizing hormone levels are in the normal range for age, whereas serum follicle-stimulating hormone levels are increased. In general, Leydig cells, with their slow rate of turnover, are much less vulnerable to damage from cancer therapy than are germ cells.[34] The risk of Leydig cell dysfunction after radiotherapy is inversely related to age and directly correlated with the radiation dose to testes; patients receiving doses of <12 Gy usually do not require testosterone replacement therapy, but doses of >20 Gy will cause Leydig cell failure in most pre-pubertal boys and doses >30 Gy in most pubertal boys and young adults.[34–37] Sperm counts do not decrease immediately after cytotoxic treatment. Sperm counts may remain normal during the first 4–8 weeks after chemotherapy. Spermatogenic stem cells are more sensitive to chemotherapy and radiation than later stage germ cells, which continue to mature into spermatozoids. Recovery of spermatogenesis depends on the type of disease and pretreatment sperm concentrations are the most significant predictors for post-treatment recovery.[38]

Spermatogenesis recovery in HCT recipients—The incidence of azoospermia after TBI may be overestimated because of the shorter follow-up in prior studies (<10 years). Rovo *et al.* reported recovery of spermatogeneis in 22% of patients after a median follow-up of 9 years after HCT.[27] Similarly, Savani *et al.*[28] reported 25% of patients showed some evidence of recovery in young patients surviving 10 years post HCT. Many patients on these studies received TBI doses of >1200 cGy. Male recipients surviving more than 10 years, younger than 25–30 years at HCT and without chronic GVHD have a reasonable likelihood of spermatogenesis, including patients receiving myeloablative TBI-based conditioning.[27,28] However, recovery can be incomplete resulting in oligospermia. High success rates reported using intracytoplasmic sperm injections suggest any recovery offers patients the opportunity to father a child.[39]

In summary, gonadal damage following HCT results in a spectrum of gonadal function with varied clinical outcomes.[4,19,35,40–46] Analysis of the contribution of conditioning regimens to gonadotoxicity may be confounded by the disease itself or prior exposure to cytotoxic agents.[30,43,47–49]

SUCCESSFUL PREGNANCY OR FATHERHOOD AFTER HCT

Multiple case reports and case series as well as registry-based reviews have described pregnancy outcomes among HCT recipients, and overall, pregnancy outcomes appear to be reassuring (Table 1).[2,19,20,50,51] The true magnitude of fertility recovery following HCT will always be difficult to determine, mainly because of incomplete data on pre- and post-transplant fertility status, but also because patient wishes regarding parenthood are frequently not known.

Most pregnancies reported by HCT survivors and their partners result in a live birth. However, in female HCT survivors who are exposed to TBI, there appears to be an increased risk of preterm delivery and delivery of low-birth-weight infants. This is consistent with previous findings in the literature on childhood cancer survivors and is thought to be related to radiation-induced structural changes in the uterus.[52–54] In addition, female HCT survivors are at higher risk of undergoing cesarean section compared with the normal population.[50] This observation may be related to the perception that transplant survivors are higher risk and therefore pregnancies are managed differently than the general population. HCT survivors have miscarriage rates that are similar to those seen in the general population.[50] However, as successful pregnancies are more likely to be reported than other pregnancy outcomes, an accurate estimate of spontaneous miscarriages after HCT is lacking. Similarly, adverse pregnancy outcomes have not been reported for male survivors of HCT who father a child.[50]

The National Institute for Health and Clinical Excellence and a joint Royal College working party have published guidelines that suggest that universal access be available to sperm, egg and embryo storage for patients undergoing gonadotoxic treatments.[55] Following publication of these guidelines, a recent audit of practices relevant to the success of this approach in the United Kingdom was published.[56] The authors reported that the number of patients who recalled being counseled about the gonadotoxic effects of HCT increased from 42% before 1990 to 86% in the contemporary era. The majority of male patients (79/112) were offered sperm banking and many (42/112) then decided to opt for it. Also 33/72 women in the reproductive age group were offered embryo/gamete or tissue storage and 12 of them opted in. Collected tissue was used frequently for reproductive purposes. Pregnancies in partners of male patients who had undergone HCT were usually successful at a reported rate of 72% (18 of 25 used stored sperm). Of four female patients attempting pregnancy with frozen embryos, two were successful.

The offspring of male and female HCT recipients do not appear to be at significantly increased risk for birth defects, developmental delay or cancer.[50] There are reports of retinoblastoma in children and major birth defects after assisted reproductive technology,[53,57,58] however, no excess risk is attributed to the HCT procedure. A general recommendation is to delay spontaneous or assisted pregnancy for at least 2 years after HCT, primarily because this is the period of highest risk for relapse.

Several HCT recipients receive novel agent therapies pre- or post-transplantation (for example, tyrosine kinase inhibitors), whose impact on fertility is not well described. Partners

of men on tyrosine kinase inhibitors do not appear to be at increased risk of pregnancy-related complications, although there is insufficient data to provide adequate reassurance. Similarly, women should avoid pregnancy while taking tyrosine kinase inhibitors.

FERTILITY PRESERVATION TECHNIQUES

Referral to a reproductive endocrinologist or infertility specialist should ideally be a part of a comprehensive treatment plan at the time of cancer diagnosis.[59–61] In addition, fertility preservation should be routinely discussed with appropriate patients at the time of pre-transplant consultation. For clinicians, it is important to have a fundamental understanding of the fertility preservation techniques that are currently available as well as the feasibility of these interventions for a given patient, based on the urgency to proceed with transplantation and presence of coexisting morbidities. In addition, an awareness of future techniques for assisting reproduction or preserving reproductive potential and currently experimental research techniques that are likely to be standard in the future, would help facilitate better patient care and inform their decisions (Table 2).[8,62–68]

Adult women/pubertal females

IVF and embryo cryopreservation—The most common and well-established option for fertility preservation in women is embryo cryopreservation using IVF.

IVF involves ovulation induction with hormone injections, typically composed of follicle-stimulating hormone and luteinizing hormone, although other techniques using alternative agents such as letrozole are being explored particularly for women with breast cancer who seek fertility preservation. About 10 days after initiation of these agents, an ultrasound-guided needle aspiration of mature ovarian follicles is performed. The retrieved oocytes can be incubated with a sperm sample or intra-cytoplasmic sperm injection may be performed on individual oocytes. Early embryos or blastocysts are cryopreserved, generally between days 3 and 5 after fertilization. When pregnancy is desired, the embryos can be thawed and transferred to the uterus with additional hormonal support. Success rates with this method are high, even in women with diminished ovarian reserve and with the use of thawed rather than fresh embryos. In 2009, the percentage of transfers of thawed embryos resulting in live births ranged from 26–36% depending on the age of the patient (http://www.sart.org).

Challenges of embryo cryopreservation/IVF that limit the applicability of this approach in HCT recipients include: (a) time requirement; 2–3 weeks between initial consultation with a reproductive endocrinologist and oocyte retrieval; (b) availability of a partner to serve as a sperm donor or patient willingness to accept banked sperm for fertilization of the oocyte; and (c) cost of and access to assisted reproductive services.

Anatomic approaches—These include: (a) gonadal shielding, where lead or other materials are placed over the ovaries to limit exposure to radiation. Ovarian shielding during TBI may be possible for some patients. However, longer follow-up of such patients will be required to establish whether normal pregnancy and delivery can occur without increasing the risk of leukemia relapse.[69] (b) Ovarian transposition, where the ovary is moved to another region of the abdomen out of the planned radiation field typically by laparoscopic

oophoropexy. Anatomic approaches are best utilized for patients primarily undergoing radiation-based therapies and hence, are not very effective for HCT recipients.

Hormonal therapies—The use of oral contraceptives[70] or gonadotropin-releasing hormone (GnRH) agonists to suppress ovarian function during cancer treatment is one of the simplest interventions that may preserve fertility; however, its efficacy is not well studied.[71–74] There is evidence that oral contraceptive use during chemotherapy is beneficial for patients with Hodgkin's disease.[70] A major limitation of current data is that most studies have exclusively enrolled women with breast cancer (with inconsistent results), where the risk of infertility may vary based on the markedly different chemotherapy regimens used in this setting compared with HCT. Hormonal therapies such as GnRH agonists or antagonists and/or oral contraceptives should not be viewed as sufficient by themselves to serve as a fertility preservation option in HCT recipients, but their use will not diminish fertility. However, pharmacologic ovarian suppression (GnRH agonist) is associated with bone loss, potentially causing additional complications in HCT recipients. GnRH analogs have been shown to reduce menstrual bleeding during cancer therapy and may be useful for that purpose in the HCT population.

Oocyte cryopreservation—Oocyte cryopreservation is a technique that is increasing because of technical improvements regarding vitrification (rapid freezing) that has improved survival rates.[75] With this method, women undergo assisted reproductive techniques including ovulation induction and oocyte retrieval. However, in contrast to embryos, oocytes present a greater challenge in terms of cryopreservation because the individual cells are larger and thus more fragile than embryos making them more susceptible to damage during the freezing and thawing process.[76,77] The major advantage of this procedure over embryo cryopreservation is the lack of need for fertilization, thus enabling access to fertility preservation for women without partners and those who are unwilling to use donor sperm. Disadvantages are similar to embryo cryopreservation, including a delay in initiation of treatment, the need for hormonal exposure, and cost and access to IVF.

Ovarian tissue banking—The need for ovarian stimulation with embryo and oocyte cryopreservation can delay treatment for 2–4 weeks, which is usually not practical for most leukemia patients. Ovarian tissue banking is experimental, but eliminates the need for ovarian stimulation and does not require a sperm source. Live births have been reported following ovarian tissue banking and transplantation in cancer patients.[78] Criteria and eligibility for ovarian tissue banking have been reported and need to be reviewed in consultation with the reproductive and fertility team.[64]

This procedure involves laparoscopic harvesting of either the whole ovary or a significant proportion of the cortex of one ovary where the maturing follicles are located.[79] Once the planned gonadotoxic therapy is completed, the ovarian tissue can be reimplanted. Reimplantation sites vary from orthotopic (replacement onto the other ovary or the peritoneum of the ovarian fossa) to heterotopic (in the subcutaneous tissue of the abdominal wall or forearm). Return of ovarian activity generally occurs within 3–6 months. In the case of orthotopic autotransplantation of ovarian tissue, conception may occur naturally and live births have been reported. Heterotopically placed ovarian tissue has to be accompanied by

IVF after ovulation induction and oocyte retrieval. There is concern regarding the potential for reseeding tumor cells following ovarian transplantation procedures in cancers that can involve the ovary, such as leukemia.[80] Therefore, transplantation of ovarian tissue is not recommended in patients with a history of leukemia or the preserved ovarian tissue should undergo minimal residual disease testing before reimplantation using the most sensitive methods available. Techniques to investigate minimal residual disease (especially histology) have proven not to be 100% sensitive.[81] Moreover, there is a so-called 'sample bias', that is, leukemic cells can be present in one piece of ovarian tissue and absent in the next piece of the same ovary. Nevertheless, cryopreservation of ovarian tissue can be offered to patients with leukemia if they are aware of the aforementioned problems, especially in children, who have limited fertility preservation options available. In the future, *in vitro* maturation may be an option for survivors of leukemia who have stored ovarian tissue.

Adult men/pubertal males

Sperm banking—For adult male patients, by far the most straightforward to fertility preservation is banking of sperm. All adolescents and young adults facing cancer therapy should be offered sperm cryopreservation as a way to preserve future fertility. Despite the fact that this method is readily available, relatively inexpensive and entirely noninvasive, numerous studies have shown that a significant proportion of male patients do not recall having been counseled regarding this method of fertility preservation.[82,83]

Unfortunately, men with cancer may not be able to bank sperm for a variety of reasons. In one study, up to 77% of men with cancer (testicular or lymphoma) who were referred for sperm banking had decreased sperm mobility[84] and another study reported 12% of men were unable to bank sperm at all due to azoospermia (10%) or inability to ejaculate due to emotional stress (2%).[33] Ideally, multiple samples should be cryopreserved before cancer treatment has begun. In situations where self-stimulation is unsuccessful, vibratory stimulation, electroejaculation or surgical sperm extraction may be used to obtain sperm.[85–88]

In adolescent boys, sperm cryopreservation is underutilized partly due to inconsistencies in fertility counseling and unclear guidelines regarding who should bank sperm.

Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of cancer therapy or HCT, and hence, it is strongly recommended that sperm be collected before starting therapy.

Anatomic approaches—Gonadal shielding is also an option for men receiving radiation therapy. In this approach, the testes are covered with lead or other material to prevent radiation from damaging testicular tissue. As with ovarian shielding, testicular shielding is not always effective because of radiation scatter, and is primarily appropriate for men who are receiving localized cancer therapies.

Pre-pubertal children

There are no standard of care methods for preserving fertility in pre-pubertal children. Gonadal tissue banking is being investigated as an option for fertility preservation in both

pre-pubertal boys and girls.[89] There is more experience with ovarian tissue banking/cryopreservation in children of young age compared with testicular banking and is the only method available for fertility preservation in pre-pubertal girls.[90–93]

Fertility preservation in pre-pubertal boys remains problematic and is an active area of investigation. Extracting and cryopreserving spermatogonial stem cells from boys can be performed for autografting at a later time. Alternatively, spermatogonia can be matured *in vitro* for use in cycles of *in vitro* fertilization.[94,95] Although transplantation of cryopreserved testicular tissue has been successful in mice and rats, data in humans are lacking.[96,97] Preserved testicular tissue should undergo minimal residual disease testing before reimplantation using the most sensitive methods available.

There are a number of special considerations for minors including provision of assent and/or consent for a procedure of value in the distant future, the use of elective surgery in young children even with minimal risks, and the fact that all fertility preservation techniques in pre-pubertal children are experimental. It can be challenging to hold the best interests of the current child and the future, theoretical adult simultaneously. Recent reviews by bioethicists conclude there are no ethical objections to providing fertility preservation services to children with cancer, if the goal is to preserve fertility options for the child when he or she reaches adulthood and not for the use of others.[98–100]

ETHICAL, FINANCIAL AND EMOTIONAL ISSUES RELATED TO FERTILITY PRESERVATION IN HCT RECIPIENTS

With improving outcomes after HCT, there are emerging issues and paradigms that have an important role in developing a comprehensive therapeutic plan for patients. Although these focus on quality of life after cancer, including the preservation of fertility, they can be associated with significant financial and emotional costs to the individual, the family and the society as a whole. As a treating clinician, it is our responsibility to discuss the possibility of infertility with all patients of child-bearing age or parents of children who face the risk, and refer interested patients to reproductive endocrinologists/infertility specialists. It may be important for treating physicians to be aware of the ethical issues surrounding fertility preservation in HCT, although there are other qualified experts (for example, hospital ethics committee) to whom patients may be referred for in-depth discussion. Costs of infertility therapy and the legal aspects that govern this issue are clearly a function of the country where a patient resides, the societal norms and the personal faith beliefs of the patient and family.

An attempt at understanding the complexity of issues that patients and their health-care providers must consider should take into account the socio-demographics of the patient (for example, age, marital status). Furthermore, patient's prognosis and other long-term quality-of-life variables that could have a bearing on the success of the assisted reproductive procedure should be considered. The American Society for Reproductive Medicine and some bioethicists have suggested that posthumous reproduction is the right of the patient and that patients with poor prognosis should still be informed of fertility preservation options.[101] Patient age is both a consideration for the ability to provide assent/consent as well as

reproductive development.[102] In addition, any potential medical risks from the fertility preservation methods (for example, ovarian hyperstimulation) should be taken into account before its use. It should be noted that for inherited syndromes, which predispose to cancer, pre-implantation genetic diagnosis is an established practice and can be considered for the patient's future offspring.[102,103]

There are significant financial considerations for patients and their families to consider regarding fertility preservation and storage. Currently, most US-based insurance companies do not cover fertility preservation procedures for cancer patients, although this may change in the near future. Furthermore, there are additional sets of costs when a patient goes on to retrieve and utilize the banked gametes, which could factor into their decision. Cultural and socioeconomic factors, sexual preference and religious factors can also impact patient decisions about assisted reproductive choices. However, it should be clear that patients should indicate whether they wish to be referred and that no bias in referrals for fertility preservation should exist based on factors related to the physician.[104,105]

In order to balance hope, quality of life and health, clinicians should understand that young patients will wish to appreciate the fullness of their future and not just have to cope with preserving their life in the present. A multidisciplinary and thoughtful approach to these considerations is tantamount to good clinical practice and patient care.

RECOMMENDATIONS TO IMPROVE REPRODUCTIVE OUTCOMES

It must be recognized that retrospective reports of pregnancy after HCT are limited by inherent bias and do not determine whether patients have actually tried to conceive and have experienced difficulty, or whether HCT survivors simply are less likely to attempt pregnancy. Moreover, there are limited data assessing the reproductive risk of newer reduced toxicity conditioning regimens. Although lower intensity conditioning regimens with exposure to no or reduced dose TBI appear to be less deleterious to reproductive function, more research is needed to determine which regimens are least gonadotoxic but clinically effective. Therefore, there is an urgent need to conduct research into various aspects of reproductive health in the transplant population. Furthermore, more data are needed to determine whether ovarian suppression during HCT decreases risk of reproductive and/or gonadal failure. For most late effects that may appear after HCT, surveillance and preemptive interventions are undertaken during long-term follow-up after transplantation. In contrast, fertility preservation methods need to be decided and implemented before HCT, and even before initiation of cancer treatment. We recommend that clinicians refer patients for fertility preservation at the earliest stage possible in their treatment and ideally before transplantation. Additional resources that clinicians can use to educate themselves and their patients about fertility preservation are listed in Table 3.

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Table 1

Review of case series of pregnancy after HCT

Reference	HCT type[a]	N	Median age at HCT, years	Median time between HCT and pregnancy, years	TBI in conditioning (%)	CY in conditioning (%)	Pregnancies resulting in live births (%)	Remarks
Sanders *et al.*[19]	Allogeneic	Women =41	18	<1–17[b]	32	100	79	Rates of abortion and congenital abnormalities no greater than general population rates Greater than expected rates of preterm deliveries and low-birth-weight infants in female HCT recipients TBI increased risk of abortion
		Men =35	22	<1–18[b]	14	100		
Jackson *et al.*[51]	Autologous	Women =10	25	2	0	0	100	No congenital abnormalities observed
Salooja *et al.*[50]	Allogeneic	Women =74	19	6	43	92	87	Rates of congenital abnormalities no greater than general population TBI increased risk of maternal complications in female recipients of allogeneic HCT
		Men =93	25	5	23	70		
	Autologous	Women =39	24	3	8	13		
		Men =26	27	4	12	39		
Carter *et al.*[2]	Allogeneic	Women =4	22	—	75	75	85	Likelihood of live birth, miscarriage and stillbirth similar to sibling controls Limited to adult HCT recipients
		Men =18	27	—	72	78		
	Autologous	Women =4	27	—	50	100		
		Men =8	30	—	25	100		
Loren *et al.*[20]	Allogeneic MA	Women =12	21	7	75	100	85% in women and 86% in partners of men	
		Men =50	25	7	44	92		
	Allogeneic RIC	Women =2	24, 33[c]	1	100	0		
		Men =2	30, 49[c]	2, 5[b]	50	50		
	Allogeneic non-malignant diseases	Women =49	18	7	6	98		

Reference	HCT type[a]	N	Median age at HCT, years	Median time between HCT and pregnancy, years	TBI in conditioning (%)	CY in conditioning (%)	Pregnancies resulting in live births (%)	Remarks
		Men =30	22	9	0	97		
	Autologous	Women =20	22	6	0	80		
		Men =13	28	7	8	77		

Abbreviations: HCT =hematopoietic cell transplantation; MA =myeloablative; RTC =reduced-intensity conditioning.

[a] All series have primarily focused on myeloablative HCT recipients except for the study by Loren *et al*.

[b] Range, median not reported.

[c] Patient age, median not reported because of only two observations.

Table 2

Recommendations for fertility preservation in HCT recipients

Recommendations
Address fertility preservation in all children and in all adult patients in the reproductive age group before starting therapy for cancer or other underlying disease, with referral to a reproductive specialist for patients interested in fertility preservation.
Address fertility preservation in all children and in all adult patients in the reproductive age group before HCT, with referral to a reproductive specialist for patients interested in fertility preservation.
Fertility preservation methods for pubertal females
Standard methods: *in vitro* fertilization and embryo cryopreservation, oocyte cryopreservation.
Experimental methods: ovarian tissue banking.
Fertility preservation methods for pubertal males
Standard methods: sperm banking.
Experimental methods: testicular tissue cryopreservation.
Fertility preservation methods for pre-pubertal females and males
Standard methods: none.
Experimental methods: gonadal tissue banking.

Abbreviation: HCT =hematopoietic cell transplantation.

Table 3

Additional resources for fertility preservation options

Organization and web links
American Fertility Association: http://www.theafa.org
American Society of Clinical Oncology: http://www.asco.org/guidelines/fertility
American Society of Reproductive Medicine: http://www.reproductivefacts.org
Fertile Hope: http://www.fertilehope.org
International Council on Infertility Information Dissemination: http://www.inciid.org
Oncofertility Consortium: http://www.myoncofertility.org
RESOLVE: the National Infertility Association: http://www.resolve.org