

IN THE NAME OF GOD



**Fertility preservation in
Pediatric Cancer & HSCT**

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Current standing and future directions in pediatric oncofertility: a narrative review .

Glen A. Lau . *Transl Androl Urol* . University of Utah, Salt Lake City. 2018 .USA.

Emily Delgouffe . *Front in Endocrinol*. 2022. Belgium.

Sigal Klipstein. *PEDIATRICS* Volume 145, nu 3, Mar 2020. Ohio.USA

- ❑ Survival rates have **improved dramatically** in the last few decades with an overall **5-year survival of 83.5% in pediatric cancer**
- ❑ Childhood cancer affects **1 /285 children < than 20 y** in the **US**, there are currently **> 375 000 survivors** of **childhood cancer** in the **US** , **with 70%** of them being **20 years or older**.
- ❑ **Europe:35,000** new cases of childhood & adolescent cancer/ Year, . Nearly **half a million** cancer survivors **in 2020**

**Current standing and future directions in pediatric oncofertility:
a narrative review .Glen A Lau . *Transl Androl Urol* . University of Utah, Salt Lake
City, UT,2018. USA**

Late Effects :

- ❑ The infertility risk resulting from gonadal dysfunction following treatments is of major concern given its high impact on the **quality of life**
- ❑ The risk of infertility is **2.5 times higher** in male cancer survivors than healthy siblings

**Current standing and future directions in pediatric oncofertility:
a narrative review.** *Glen A . Transl Androl Urol . University of Utah, Salt Lake City,
UT, USA*

- ❑ **While fertility may not be the most pressing issue in the management of pediatric patients with newly-diagnosed cancer**, it has been demonstrated that as survivors aged, they and their families had significantly more interest in fertility
- ❑ Parents and adult survivors of childhood cancer were also shown to have a significant amount of **regret** when FP was not pursued at the time of initiation of therapy

Oncofertility in pediatric patients

Rafael Marques. Portugal.2022

Delgouffe et al. Frontiers in Endocrinology . Belgium. 2022

- ❑ **MALIGNANCY : LEUKEMIA , Lymphoma** (10% azoospermic pretreatment)
- ❑ **Cancer treatment : Chemo , Radiation & Surgery**
- ❑ Pro inflammatory cytokines;(IL-6,IL-8, and TNF- α) impairs the **blood-testis barrier & germ cell apoptosis**
- ❑ Severe malnutrition and fever (spermatogenesis & changes in sperm motility)
- ❑ Pain, anorexia, psychological effects
- ❑ **HSCT : (Malignant & non malignant disease) Chemo condition (MAC/RIC) & TBI**

Infertility due to cancer

- Infertility due to cancer treatment is multifactorial
- The incidence of infertility in patients receiving Chemo- and Radiation therapy varies widely with Age & Gender, but remains significant
- Younger patients :lower risk than older patients
- Female patients ;lower risk

Categorizes the likelihood of **infertility**

American Society of Clinical Oncology ASCO

- likelihood of **infertility** based on various chemotherapeutic regimens into:
 - **Low Risk (<20%)**
 - **Intermediate Risk (20–80%)**
 - **High Risk (>80%)**

Chemotherapeutic agents & Gonadotoxicity.

Onco fertility in pediatric patients: current perspectives.

Rafael Marques 1.2022

High risk	Medium risk	Low or no risk	Unknown risk
Nitrogen mustard	Vinblastine	Methotrexate	Paclitaxel
Chlorambucil	Cytosine arabinoside	5-fluorouracil	Taxotere
Cyclophosphamide	Cisplatin	6-mercaptopurine	Oxaliplatin
Melphalan	Carboplatin	Vincristine	Irinotecan
Busulfan		Bleomycin	Trastuzumab
Procarbazine		Actinomycin D	Pertuzumab
Dacarbazine			Cetuximab
Doxorubicin			Erlotinib
Carmustine			Daunorubicin
Lomustine			Imatinib

Estimated risk of prolonged azoospermia with chemo- and radiotherapy. Indications for Testicular Tissue Banking.

Delgouffe et al. Frontiers in Endocrinology . Belgium. 2022

	High risk (indication for TT banking)	Medium risk	Low risk
Chemotherapy	Busulfan >600 mg/m ² (5, 7, 58)	Carboplatin >2 g/m ² (5, 7, 58, 68)	Actinomycin-D UD (5, 7)
	Carmustine 1 g/m ² (5-7, 69)	Cisplatin 400-600 mg/m ² (5, 7, 58)	Azathioprine UD (7, 69)
	Chlorambucil >1.4 g/m ² (5-7, 58, 68, 69)	Cyclophosphamide 7.5-19 g/m ² (5)	Bleomycin UD (5-7, 58, 68, 69)
	Chlormethine UD (7, 58, 69)	Cytarabine 1 g/m ² (7, 68)	Cytarabine <1 g/m ² (5)
	Cisplatin >600 mg/m ² (5-7, 68, 69)	Dacarbazine UD (7, 69)	Dactinomycin UD (58, 68)
	Cyclophosphamide >19 g/m ² (5-7, 58, 68, 69)	Daunorubicin UD (7, 69)	Etoposide UD (5-7, 68, 69)
	Ifosfamide >52 g/m ² (5-7, 58, 68)	Doxorubicin >770 mg/m ² (5-7, 58, 68, 69)	Fludarabine UD (7, 69)
	Lomustine 500 mg/m ² (if treated before puberty) (5, 6)	Gemcitabine UD (7, 69)	5-Fluoracil UD (5, 6, 69)
	Mechlorethamine UD (7, 68)	Ifosfamide 42-52 g/m ² (5)	6-Mercaptopurine UD (5-7, 58, 68, 69)
	Melphalan >140 mg/m ² (5-7, 58, 68, 69)	Mitoxantrone UD (7, 69)	Methotrexate UD (5, 6, 58, 68, 69)
	Mustine UD (7)	Oxaliplatin UD (7, 68, 69)	Vinblastine 50 g/m ² (5-7, 58, 68, 69)
	Procarbazine >4 g/m ² (5-7, 58, 68, 69)	Thiotepa 400 mg/m ² (5, 7, 69)	Vincristine 8 g/m ² (5-7, 58, 68, 69)

Radiation

- ❑ Radiation therapy also :significant effect on fertility with cumulative
Over 4 Gy to the testes , 30 Gy to the hypothalamus-pituitary axis, and
>5 Gy to the uterus and/or ovaries
- ❑ **Testicular tissue is extremely radiosensitive;**
- ❑ Doses; 0.1-1.2 Gy :temporarily **oligo- or azoospermia**
- ❑ Doses 2-3 Gy affect the **Spermatogonial stem cells (SSCs)**,
causing **long-term infertility**
- ❑ Doses of **6 Gy and more completely deplete the SSC pool** and
lead to **permanent azoospermia**

Estimated risk of prolonged azoospermia with chemo- and radiotherapy. Indications for Testicular Tissue Banking.. Delgouffe et al. Frontiers in Endocrinology .Belgium. 2022

High risk (indication for TT banking) / **Medium risk** / **Low risk**

Radiotherapy	High risk (indication for TT banking)	Medium risk	Low risk
	Total body irradiation (5, 7, 58)	Craniospinal- and cranial radiotherapy ≥ 25 Gy (5, 58, 70)	Lower radiation doses
	Testicular radiotherapy (5, 7, 58, 70)	Scattered abdominal or pelvic radiation ≥ 1 Gy (5)	

Targeted Therapy.

Delgouffe et al. *Frontiers in Endocrinology*. 2022. Belgium

- Briefly; **Imatinib, Dasatinib, Gemtuzumab**; some adverse effects on the **reproductive health in rat studies**
- **Imatinib in adult human studies**; Oligozoospermia , using of Imatinib during **prepuberty**
- **Nilotinib, Nivolumab, Rituximab, Dinutuximab, Blinatumomab, Tisagenlecleucel (Car T-cell Therapy)**, no adverse effects on fertility were found so far. More studies are needed.

Onco fertility

- ❑ The American Society of Clinical Oncology (ASCO) first published guidelines recommending that referral for fertility preservation (FP) be offered to patients of reproductive age in 2006
- ❑ Numerous guidelines and recommendations have been published.
- ❑ **Some that address pediatric patients**
 - **Few advances in clinical practice have been realized in the last decade. Awareness of the issue has increased, practice patterns regarding discussion of FP with appropriate patients varies widely even among oncologic specialists**

Fertility preservation in pediatric leukemia and lymphoma:

A report from the Children's Oncology Group Allison Close. **Pediatr Blood Cancer. 2023;70**

□ lack of standardization

- **In 2020**, the **Pediatric Initiative Network (PIN)** of the Oncofertility Consortium created a working group of **27 clinicians and researchers from 15 institutions** : **literature review** : consensus around **levels of gonadotoxic risk related to treatment exposure** (*reducing variability between providers and across institutions.*)

Fertility preservation in pediatric leukemia and lymphoma: A report from the COG .Allison Close. Pediatric Blood and cancer . Aug .2023.USA

- ❑ **Phase III COG ;Leukemia / Lymphoma protocols** instituted in 2000 - 2022
- ❑ **Gonadotoxic risk;** (Alkylating agents, heavy metals, HSCT, or Hypothalamic or Gonadal Radiation).
- ❑ **High-risk therapy ;**that exceeds a **CED(Cyclophosphamide equivalent dosing):** 4 gm/m² in males 8 gr/m² in pubertal females, 12 gm/m² in prepubertal females
- ❑ **Any HSCT (Myeloablative or/ Reduced intensity)** containing at least one alkylating agent or total body irradiation (TBI)
- ❑ **Also High-risk therapy :Gonadal Radiation (Direct or Indirect)** 15 Gy or higher in prepubertal females,10 Gy or higher in pubertal females, and 4 Gy or higher in males

Level of risk for gonadal failure/infertility above that of the general population: (A) female risk level; (B) male risk level. CED: cyclophosphamide equivalent dosing; RPLND: retroperitoneal lymph node dissection. CLOSE ET AL. pediatric Blood and cancer.2023

(A)

Female Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m2	Prepubertal		CED < 8	CED 8-12	CED >12
	Pubertal		CED <4	CED 4-8	CED > 8
Heavy Metal mg/m2			Cisplatin Carboplatin		
Hematopoietic Stem Cell Transplant					Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Radiation Exposure	Ovary	Prepubertal		<15 Gy	≥ 15 Gy
		Pubertal		< 10 Gy	≥ 10 Gy
	Hypothalamus		22-29.9 Gy	30-39.9 Gy	≥ 40 Gy

(B)

Male Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m2			CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant					Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Heavy metal mg/m2			Cisplatin Carboplatin	Cisplatin >500	
Radiation Exposure	Testicular		0.2-0.5 Gy	0.7-3.9 Gy	≥ 4 Gy
	Hypothalamic		26-29.9 Gy	30-39.9 Gy	≥ 40Gy
Surgery				RPLND	

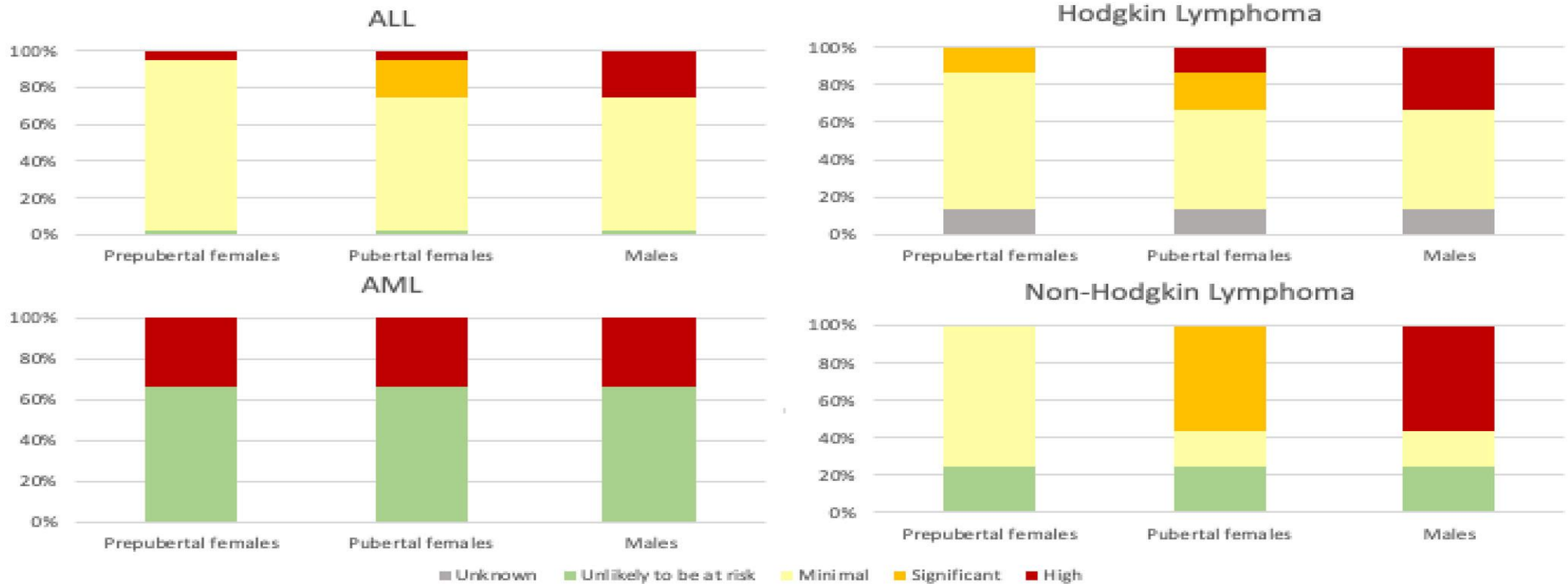
Fertility preservation in pediatric leukemia and lymphoma: A report from the Children's Oncology Group Allison Close. Pediatric Blood and cancer . 2023

RESULTS ;26 protocols with 97 treatment

- Male most commonly at *high* risk: (53.8%)
- pubertal females:(23.1%)
- pre pubertal female : 15%
- **All patients with direct gonadal Radiation or (HSCT); *High risk***

Distribution of risk levels for treatment-related gonadal failure/infertility for (COG) treatment. Protocols 2000–2022.

CLOSE ET AL. pediatric Blood and cancer.2023



RECOMMENDATIONS

Fertility Preservation

We can help you overcome the complications of infertility associated with chemo and radiation therapy.



Fertility preservation in pediatric leukemia and lymphoma: A report from the Children's Oncology Group

Allison Close. Pediatric Blood and cancer . Aug .2023

- Recommendation : counseling all patients
- **Risk tables** Gonadal dysfunction/infertility: **allows for quick identification of patients who are at *high* or *significant* risk,**
- **Team work :Oncology, Surgical subspecialties (gynecology, urology, pediatric surgery, reproductive endocrinology), patient navigators/educators, and survivorship teams**

Males, Pubertal

- Pubertal males, semen cryopreservation (or sperm banking) is

the gold standard method of fertility preservation (masturbation, testicular sperm extraction (TESE) or electroejaculation)

- Consults for pubertal males need to be done in a **timely** fashion to **allow for collection to be completed prior to receiving chemotherapy**

Male pre-pubertal patients :Cryopreservation of gonadal tissue.

- 2002 first program
- pre-pubertal patients diagnosed with cancer currently have no proven option of FP
- At this time, TTC is considered an experimental method of fertility Preservation
- TTC should only be offered to high-risk patients

prepubertal Male TT c

- ❑ **Wedge biopsy** of **testicular tissue** /under **general anesthesia/Cryopreservation**

3 restoration methods currently under development:

- ❑ 1) auto-transplantation of the thawed TT
- ❑ 2) auto-transplantation of isolated SSCs from the TT
- ❑ 3) in vitro spermatogenesis.
- ❑ **Hematologic malignancies, risk of contamination**

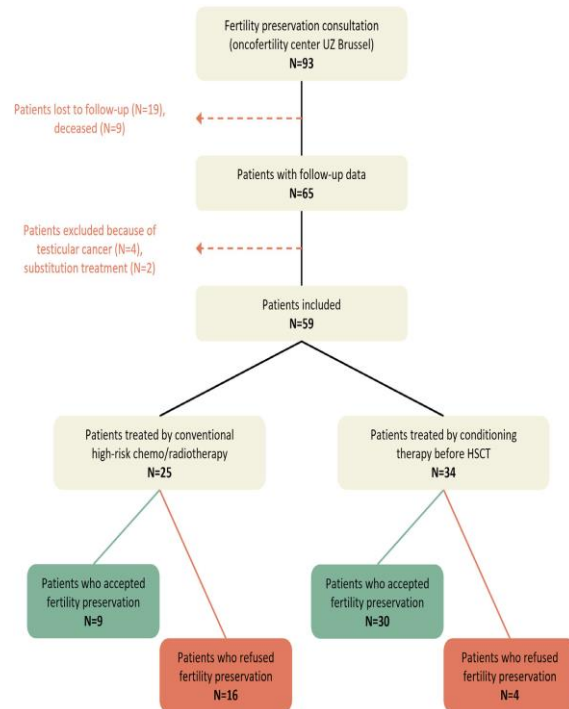
prepubertal Male TT c.

Allison Close. Pediatr Blood Cancer. 2023;70:e30407. ■

- Unilateral TT biopsy during childhood does not appear to adversely affect the **reproductive health outcomes**.
- **TT biopsy**: Short-term complication risk of 2-3%
- Only a few studies investigated the possible **adverse effects** in the **longer term**.
- **At the time of published this paper (2023) ,there have been no human births from this method; however, there have been many promising animal models including non-human primates**

Gonadal development and function after **immature testicular tissue banking** as part of **high-risk gonadotoxic treatment**.

Pediatric Blood and cancer. Aude Braye. Aug 2023. Belgium



- ❑ The clinical follow-up data demonstrate no effect related to the biopsy procedure
- ❑ A substantial risk for impaired gonadal development after **high-risk gonadotoxic treatment**, in particular MAC-HSCT.
- ❑ Longer follow-up studies with a larger study population are needed to confirm these preliminary findings

Guidelines from ASCO Female patients

- More resistant to deleterious effects of chemotherapy
- Radiation therapy and chemotherapy: increase risk of premature ovarian failure

Pubertal Females

- ❑ Options ; Oocyte / Embryo Cryopreservation & ovarian tissue cryopreservation (OTC).
- ❑ **Standard :Oocyte or Embryo Cryopreservation**
- ❑ Utilizing injectable **Hormones to stimulate** the growth of multiple **follicles stimulation**
- ❑ Harvest of oocytes& **Frozen as an unfertilized oocyte or as a fertilized embryo.**
- ❑ Process of stimulation & oocyte collection takes : 2 weeks
- ❑ **Time ?????**

pubertal Females

- Next Option for CP: ovarian tissue cryopreservation (OTC)
- **OTC is the only option for prepubertal females**
- OTC ; laparoscopic removal of one, **or part of one ovary** that is then **processed** into small cortical strips and **cryopreserved**.
- Reimplantation in the **peritoneal cavity** or on the **remaining ovary**.

Fertility preservation in pediatric leukemia and lymphoma: A report from the Children's Oncology Group .

Allison Close. 2023 . pediatric blood and cancer

- ❑ Since 2004, over 130 live offspring have been born via reimplanted ovarian tissue;
- ❑ However, the vast majority of these cases were from **tissue harvested in patients who had already gone through puberty and achieved menarche**
- The experience with reimplanting tissue for **prepubertal patients is very limited** and the success of OTC in **younger patients remains unknown**

Tissue cryopreservation to pre-pubertal patients

- Survey of members of the Oncofertility Consortium
Global Partners Network ;
 - 16 centers worldwide offer **testicular tissue cryopreservation**
 - 26 centers offer **ovarian tissue cryopreservation to pre-pubertal patients**

Barriers in Fertility Preservation

- ❑ Younger age & Female
- ❑ Patient and parental factors, How to approach a conversation about FP
- ❑ **Facilities and specialists for FP referrals (Team work Oncology-Endocrinology and Reproductive Medicine Center)**
- ❑ Ethical issues remain with children and adolescents particularly those in the pre-pubertal period.
- ❑ **The cost and details of FP procedures**

A Prospective Study on Fertility Preservation in Prepubertal and Adolescent Girls Undergoing HSCT . Ida Wikander. ORIGINAL RESEARCH.2021

- In **Sweden** and the other Nordic countries, **programs for fertility preservation / free of charge.**
- The Fertility Preservation Program at the Reproductive Medicine Clinic of **Karolinska University Hospital** was initiated in the **1970's** when methods for freezing sperm first became available.
- **1998 ;Cryopreservation of Embryos, Ovarian tissue & thereafter Oocytes**

A Prospective Study on Fertility Preservation in Prepubertal and Adolescent Girls Undergoing HSCT. Ida Wikander. ORIGINAL RESEARCH.2021

Results:, **34/39** girls and adolescents :**FP-** before or after HSCT.

- ❑ **Before HSCT, ovarian tissue in 15 p& oocytes preserved in 2 patients**
- ❑ **After HSCT:13 ovarian tissue & 7 patients cryopreserve oocytes.**
- ❑ **Follicles were present in all tissue samples collected prior to HSCT, and in more than ½ half of the samples collected post-HSCT.**
- ❑ Half of the patients had spontaneous menarche or resumed menstruation post HSCT.
- ❑ **7 patients had achieved parenthood.**

Fertility preservation in HSCT

- ❑ Fertility preservation treatments can be performed both before and after HSCT.
- ❑ *Oocyte cryopreservation might still be the preferred option for fertility preservation*
- ❑ **Cryopreservation of ovarian tissue** ;successful pregnancy and should be encouraged in **young women and cases with time limitations**

Fertility preservation in pediatric HSCT

Published: 24 July 2017

Transplant Toxicities

Fertility preservation issues in pediatric hematopoietic stem cell transplantation: practical approaches from the consensus of the Pediatric Diseases Working Party of the EBMT and the International BFM Study Group

[A Balduzzi](#) , [J-H Dalle](#), [K Jahnukainen](#), [M von Wolff](#), [G Lucchini](#), [M Ifversen](#), [K T Macklon](#), [C Poirot](#), [T Diesch](#), [A Jarisch](#), [D Bresters](#), [I Yaniv](#), [B Gibson](#), [A M Willasch](#), [R Fadini](#), [L Ferrari](#), [A Lawitschka](#), [A Ahler](#), [N Sanger](#), [S Corbacioglu](#), [M Ansari](#), [R Moffat](#), [A Dalissier](#), [E Beohou](#), on behalf of the Pediatric Diseases

Working Party of the European Society for Blood and Marrow Transplantation and the International BFM Study Group [+ Show authors](#)

[Bone Marrow Transplantation](#) **52**, 1406–1415 (2017) | [Cite this article](#)



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Full Length Article

Brief Article

Safety of Surgical Fertility Preservation Procedures in Children Prior to Hematopoietic Stem Cell Transplant



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Safety of Surgical Fertility Preservation Procedures in Children Prior to Hematopoietic Stem Cell Transplant.

K. Brodigan et al. / Transplantation and Cellular Therapy . 2021. Boston, Massachusetts

- ❑ **Retrospective study 2018-2020. 22 Patients aged 0 to 25 y**
- ❑ **Prepubertal and pubertal patients**
- ❑ **Malignant and non malignant disease**
- ❑ Discussion with oncofertility specialist
- ❑ Surgical fertility preservation : **Laparoscopic unilateral oophorectomy or testicular biopsy) , under general anesthesia, at the time CVL placement prior to the initiation of HSCT conditioning.**
- ❑ **The mean duration for the procedures performed, 98 minutes (49 to 260 minutes) and 97 minutes (56 to 178 minutes), for OTC & TTC respectively**

Safety of Surgical Fertility Preservation Procedures in Children Prior to Hematopoietic Stem Cell Transplant.

K. Brodigan et al. / *Transplantation and Cellular Therapy* . 2021. Boston, Massachusetts

- ❑ Children of **all ages** can now be offered the possibility of **fertility preservation** following HSCT for benign and malignant conditions
- ❑ The **procedure** for both **females and males** can be performed close to the **start of conditioning**, which allows for coupling with **central access placement**.
- ❑ These procedures appear to be **safe** and do **not add** to transplant-related **morbidity**.

Conclusion

- ❑ Fertility preservation remains **an emerging field**, particularly in the **pediatric setting**.
- ❑ FP become increasingly important to patients as they **enter adulthood** and should thus be discussed with **children and adolescents**
- ❑ Established **options for FP exist for both male and female**
- ❑ **Still Barriers remain**



THANK YOU