FPS(I)
Preserve . Create . Perpetuate

Newsletter - FSP(I)

April 2021 (Volume 2)

A very good day to all of you reading this E-Newsletter. This is FPSI's 2nd edition of the same. We are now well into the 2nd wave of raising COVID cases, but at the same time, we do hope you have all received the vaccination and hence will be protected to some extent against COVID-19.

Without much further ado, we would like to introduce our e-newsletter to you. This time we have decided to concentrate on the fertility preservation options in the younger generation – mainly children, adolescents and young adults.

The first article is a compilation from "FERTILITY PRESERVATION FOR PEDIATRIC AND ADOLESCENT PATIENTS WITH CANCER: MEDICAL AND ETHICAL CONSIDERATIONS" - Klipstein S (From the American Academy of Paediatrics)

It is a synopsis of the medical and ethical issues of fertility preservation in the Paediatric and Adolescent age group.

Need for Fertility preservation in Pediatric and Adolescent Population

- 1 in 285 children below 20 yrs of age suffer from cancer
- Survival rates are 83.3%
- Chemotherapy, Radiotherapy and hematopoietic stem cell transplant affect fertility in later life.

Counselling for Fertility preservation:

- Should start soon after diagnosis is confirmed.
- Type of malignancy, chemotherapeutic and Radio-therapeutic effects on gonads to be explained
- Survival rates depending on type of malignancy and stage of the malignancy to be emphasized
- Fertility Preservation options differ in prepubertal and post pubertal children
- Counselling should be undertaken by the Physician providing cancer treatment
- The affected child as well as parents /family members to be provided with information.

Ethical Issues:

- Consent/assent is necessary
- Decision on disposition of cryopreserved gametes (sperms, Oocytes,embryos, ovarian tissue) can be taken only after the child attains the age of major. The decision for fertilization or donation can only be given by the child after becoming major.

- In case of death of the child before the age of major (adult hood) the parents or guardian do not have the rights of using the gametes for reproduction or donation. The gametes should be discarded or destroyed. American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology have also issued similar guidelines.
- IRB approval necessary for experimental procedures of fertility preservation.
- Ovarian tissue cryopreservation for female children and adolescents and testicular tissue preservation for male children and adolescents is still considered experimental.
- Consent for disposition should be recoded and kept in the centre where gametes or tissue is stored.
- When conflicts arise between the child and parents regarding disposition of gametes, support should be given to the open future of the child while respecting family issues.
- Parents should consider child's assent, details of the fertility preservation technique and its utility while deciding to preserve fertility of the child /adolescent.

Evaluation for Fertility Preservation:

- Institution should have a policy for fertility preservation
- The policies should be formed by a team of specialists which may include Paediatric Oncologist, Reproductive Medicine specialist, Urologist with expertise in male infertility, Radiation oncologist, ethics consultant, mental health specialist and expert in reproductive Law.
- Cryopreservation of Oocytes or Sperms should be offered whenever possible for post-pubertal children
- Delay in offering fertility preservation techniques should not compromise cancer treatment
- Timely referral to centers with facility for fertility preservation.
- In case of emergency treatment for cancer, the impact of treatment on future fertility to be explained and recorded.

Fertility Preservation Options: Pre-Pubertal Children and Adolescents

Boys:

Proven: Sheiding the testes or relocating them away from radiation fields to thigh or anterior abdominal wall

Sperm cryopreservation in older adolescents who can masturbate

Experimental: Testicular tissue cryopreservation, autotransplantation or xenotransplantation or invitro maturation of spermatids

Girls:

Proven: Sheilding of Ovaries or Oopheropexy

- ✓ Ovarian transposition retains 60% of hormonal function and 15% of subjects achieved pregnancy later
- ✓ Benefit of Ovarian shielding is less effective if adjuvant chemotherapy is needed.

Pre-pubertal girls: Ovarian tissue cryopreservation – Was performed in a very young child of 2.7 years. The ovarian tissue can be thawed and auto transplanted once cured of malignancy as hormonal function to be restored.

One report of live birth in prepubertal ovarian cryopreservation (9yrs old) and auto transplantation is published.

Fertility Preservation Options: Post Pubertal adolescent

Male Adolescents:

- Sperm cryopreservation after masturbation is the most established and effective method of fertility preservation in male adolescents.
- Testicular aspiration or extraction or electro ejaculation can be performed under sedation or anaesthesia if masturbation is not possible.
- Whenever possible, sperm should be collected before initiation of cancer therapy to prevent the risk of sperm DNA integrity or compromising sample quality.
- Sperm can be collected at infertility centers or andrology laboratories and stored either at these sites or at long-term storage facilities.
- Sperm Quality is poor in Testicular cancer, leukemia and Hodgkin's disease.

Female Adolescents:

- Oocyte Cryopreservation is the recommended method
- Successful pregnancy rates by using previously cryopreserved oocytes have been reported to be as high as 50% in adult women cryopreserving their oocytes and would be expected to be even better in young women and adolescents.
- No increases in chromosomal abnormalities, birth defects, or developmental deficits have been noted in the children born from cryopreserved oocytes as compared with other standard ART procedures, such as IVF, and with natural conception. However, these data are not from patients who cryopreserved their oocytes after a cancer diagnosis
- American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists support the use of oocyte cryopreservation for women at risk for losing ovarian reserve because of gonadotoxic exposures.
- The process of oocyte cryopreservation requires approximately 10 days of monitoring with transvaginal ultrasonography and blood tests, followed by a transvaginal oocyte retrieval performed under anesthesia.
- Cryopreservation of embryos, in which oocytes are fertilized with sperm from the male partner or with anonymous donor sperm is another option

Acknowledgement

"FERTILITY PRESERVATION FOR PAEDIATRIC AND ADOLESCENT PATIENTS WITH CANCER: MEDICAL AND ETHICAL CONSIDERATIONS" Klipstein S, Fallat ME, Savelli S, AAP COMMITTEE ON BIOETHICS, AAP SECTION ON HEMATOLOGY/ONCOLOGY, AAP SECTION ON SURGERY. Fertility Preservation for Pediatric and Adolescent Patients with Cancer : Medical and Ethical Considerations. Pediatrics. Mar 2020;145(3):e20193994.

SECOND ARTICLE

FERTILITY PRESERVATION FOR FEMALE PATIENTS WITH CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER: RECOMMENDATIONS FROM THE PANCARELIFE CONSORTIUM AND THE INTERNATIONAL LATE EFFECTS OF CHILDHOOD CANCER GUIDELINE HARMONIZATION GROUP

The second article is a set of recommendations for fertility preservation in Childhood, Adolescent and Young Adult Cancer by Renee Mulder et al which is the first of a series of 3 articles published in the Lancet in February 2021.

We have made a synopsis of these guidelines only including high quality and moderate quality evidence.

Female patients with childhood, adolescent, and young adult cancer are at an increased risk for fertility impairment when treatment adversely affects the function of reproductive organs. Patients and their families desire biological children but substantial variations in clinical practice guidelines reduce consistent and timely implementation of effective interventions for fertility preservation across institutions.

To facilitate global consensus regarding this topic, the EU-funded project, PanCareLIFE, in collaboration with the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG), organised a multidisciplinary group of international experts to develop a transparent evidence-based CPG for fertility preservation in female patients with CAYA cancer.

A multidisciplinary panel of 36 international specialists in paediatric oncology and haematology, radiation oncology, endocrinology (including paediatric endocrinology), reproductive medicine, gynaecology, psychology, epidemiology, and guideline methodology was convened.

The aim of this CPG was to help health-care providers to communicate the potential risks for infertility and options for fertility preservation to both female patients who were diagnosed with childhood cancer tumour types aged 25 years or younger and to their parents, caregivers, or partners (hereafter referred to as families) and to provide guidance about how and when to offer fertility preservation treatment.

Recommendations:

Final recommendations were based on scientific knowledge combined with other considerations, including clinical judgment, costs, ethical issues, and the need to maintain flexibility across health-care systems. The recommendations were then critically appraised by three independent external experts and three patient or survivor representatives.

Who should be informed about potential infertility risk?

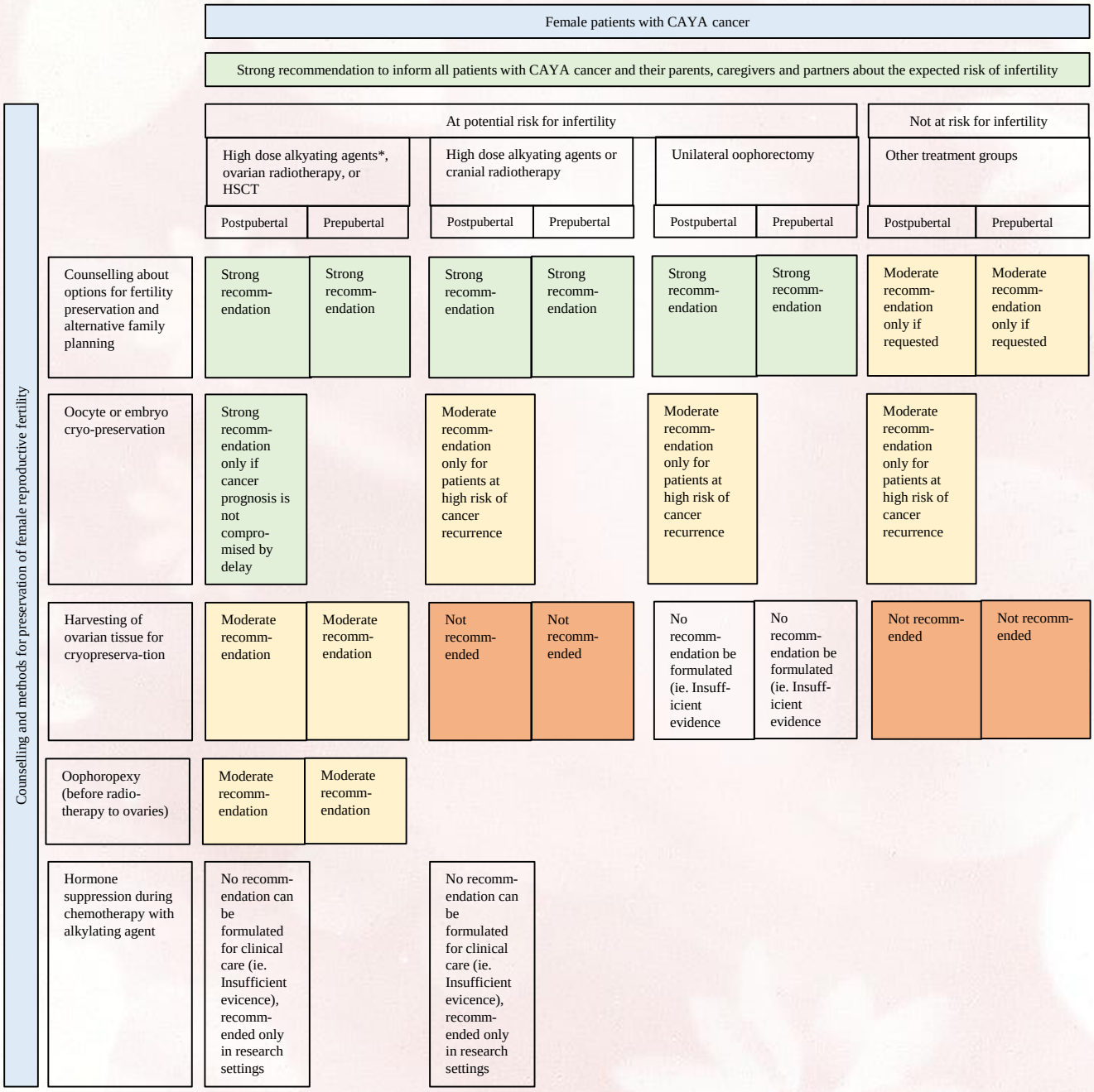
The panel agreed that all patients with cancer and their families have the right to be informed about the potential risk for infertility. Therefore, they strongly recommended that health-care providers inform all patients and their families about the expected risk of infertility or early menopause, or both, which can vary in magnitude on the basis of the specific treatment planned.

Who should be counselled about fertility preservation?

Based on previously published IGHG and newly published data, there is high-quality evidence that alkylating agents are associated with premature ovarian insufficiency in a dose-dependent manner in survivors of CAYA cancer.

It was noted that there was an increased risk of premature ovarian insufficiency with increasing doses of procarbazine (high-quality evidence) and cyclophosphamide (moderate-quality evidence). Additionally, an increased risk of premature ovarian insufficiency after treatment with busulfan was identified, but the dose–response relationship was unclear (low-quality evidence).

There was high-quality evidence that increasing doses of radiotherapy to volumes exposing the ovaries (hereafter referred to as ovarian radiotherapy) increased the risk of premature ovarian insufficiency in survivors of CAYA cancer. Treatment with a combination of alkylating agents and ovarian radiotherapy increased the risk of premature ovarian insufficiency compared with that associated with each method alone (moderate-quality evidence).



Recommendations for preservation of reproductive fertility for female patients with CAYA cancer

*Colours represent the strength of recommendation for each method on the basis of the evidence (where green indicates strong recommendation, yellow indicates moderate recommendation, and red indicates that a method is not recommended), corresponding to colours used in previous International Late Effects of Childhood Cancer Guideline Harmonization Group publications. For further details on recommendations see appendix pp 40–41. CAYA=childhood, adolescent, and young adult. HSCT=haematopoietic stem-cell transplantation. *Cyclophosphamide-equivalent dose ≥6000–8000 mg/m². †Cyclophosphamide-equivalent dose <6000–8000 mg/m².*

An association was identified between increasing doses of cranial radiotherapy and the risk of hypogonadotropic hypogonadism (moderate-quality evidence).

Recommendations

- The panel concluded that there was a high risk of premature ovarian insufficiency after cumulative doses of alkylating agent at or above the range of 6000–8000 mg/m² and a low risk of premature ovarian insufficiency for less than this range.
- Patients who were treated with ovarian radiotherapy were also at increased risk of premature ovarian insufficiency (high-quality evidence).
- The panel recognized that patients who were treated with Hematopoietic Stem Cell Transplantation (HSCT) and unilateral oophorectomy were at potential risk of impaired fertility.
- Patients who were treated with cranial radiotherapy were at risk for infertility as well. Although gonadal function was not affected, ovarian function could be impaired by damage to the hypothalamic–pituitary axis.

The panel strongly recommended that health-care providers discuss options for fertility preservation and alternative family planning with patients with CAYA cancer and their families if planned treatment include alkylating agents of any dose (high-quality evidence), ovarian radiotherapy (high-quality evidence), HSCT (very low-quality evidence), unilateral oophorectomy (very low-quality evidence), cranial radiotherapy (very low-quality evidence), or a combination.

The panel concurred that if planned treatment did not include gonadotoxic modalities, then patients with CAYA cancer and their families were to be advised of the benefits and harms of fertility preservation within the context of their personal risk. They were to also consider the risk of cancer recurrence or disease progression (i.e., absence of response to initial therapy) that might lead to a potential future need for gonadotoxic therapy.

What methods for reproductive preservation are appropriate to offer in counselling?

The panel identified oocyte and embryo cryopreservation as established methods for fertility preservation in postpubertal women. Pragmatically, most adolescents and young adults (i.e., ≤25 years) would opt for oocyte cryopreservation as they were much less likely to be partnered or interested in donor sperm than older women.

If the infrastructure for referral to reproductive endocrinology was in place, then delays could be minimal which could allay reviving concerns about cancer outcomes due to delays. Although an age cutoff for oocyte cryopreservation was difficult to define, the panel acknowledged the ethical complexities and requirements of physical and emotional maturity of postmenarcheal girls. They strongly recommended offering oocyte or embryo cryopreservation to postmenarcheal patients with CAYA cancer if prognosis would not be compromised by a delay in treatment initiation. Due to the immaturity of the oocytes, this method of fertility preservation was not an option for prepubertal and peripubertal girls.

Moderate Quality Recommendations

Fertility preservation for prepubertal girls is ethically complex because there is a scarcity of evidence about the efficacy of ovarian tissue cryopreservation for this age group. The panel agreed that collection of ovarian tissue was ethically justifiable in most circumstances and did not require additional governance.

The panel considered post pubertal autotransplantation as the only mechanism by which cryopreserved ovarian tissue could be used for fertility and this could be offered as clinical care but advised careful evaluation of outcomes of the procedure as clinical research.

The panel considered oophoropexy as an established procedure that was generally feasible before administration of pelvic radiotherapy. Consultation with a radiation oncologist was essential to establish whether oophoropexy would facilitate ovarian shielding during radiotherapy in the context of the patient's pelvic tumours, as it involve an operative procedure with its own inherent risks.

The panel agreed that hormone suppression could be offered in a research setting. If offered, it would be an adjunct to other procedures for fertility preservation and not a replacement.

As there was no evidence for gonadotoxic effects of treatments other than alkylating agents, ovarian radiotherapy, HSCT, unilateral oophorectomy, or cranial radiotherapy, they only moderately recommended offering oocyte or embryo cryopreservation to postmenarcheal patients who were at high risk of recurrence and might need gonadotoxic treatment in the future (evidence cited in existing guidelines).

Several reports from the Childhood Cancer Survivor Study evaluated multiple chemotherapeutic agents, including anthracycline agents by univariate analysis, none of which identified anthracyclines as a significant determinant for gonadotoxicity. Moreover, van den Berg and colleagues evaluated hormonal and ultrasound markers of ovarian reserve and showed no significant effect of doxorubicin on low antral follicle count.

Acknowledgement

"FERTILITY PRESERVATION FOR FEMALE PATIENTS WITH CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCER: RECOMMENDATIONS FROM THE PANCARELIFE CONSORTIUM AND THE INTERNATIONAL LATE EFFECTS OF CHILDHOOD CANCER GUIDELINE HARMONIZATION GROUP[1]." RENEE L MILDER, ANNA FONT-GONZALEZ, MELISSA M HUDSON, HANNEKE M SANTEN, ERIK H LOEFFEN, KAREN C BURNS, GWENDOLYN P QUINN, ELINE VAN DULMEN-DEN BROEDER, JULIANNE BYRNE, RICCARDO HAUPT, W HAMISH WALLACE, MARRY M CAN DEN HEUVEL-EIBRINK, ANTOINETTE ANAZODO, RICHARD A ANDERSON, ANKE BARNBROCK, JOERN D BECK, ANNELIES M E BOS, ISABELLE DEMEESTERE, CHRISTIAN DENZER, NATASCIA DI LRGI, HOLLY R HOEFGEN, REJIN KEBUDI, CORNELIS LAMBALK, THORSTEN LANGER, LILLIAN R MEACHAM, KENNY RODRIGUEZ-WALLBERG, CATHARYN STERN, EVELINE STUTZ-GRUNDER, WENDY VAN DORP, MARGREET VEENING, SASKIA VELDKAMP, ELINE VAN DER MEULEN, LOUIS S COSTINE, LISA B KENNEY, MARIANNE D VAN DE WETERING, LEONTIEN C M KREMERT, JENNIFER LEVINET, WIM J E TISSING, on behalf of the PanCareLIFE Consortium, 2021;22:e45-56.

We do hope you have enjoyed reading this compilation and found it useful. We encourage all of you to become members of FPSI as cancer is a now a household name and there are not many families who do not have or have heard of someone near or dear who have been afflicted with cancer. So we are going to be confronted with these problems increasingly and being part of the society will help you to widen your knowledge horizons and also have a healthy discussion when in doubt as to the way forward in any clinical situation….. So do join us.

The membership form can be downloaded by clicking the following link.

Membership Form

We would also like to encourage you to talk about you experience dealing with cancer patients in the form of case reports, case series and review articles and submit them to TOGF on the below link.

https://www.tofjonline.org/

Please tune in to our next webinar on Fertility Preservation in Breast Cancer on 01st May 2021, 05.00pm onwards.

The tentative programme is as below:

FACULTY

1. Dr. Selvi Radhakrishna
2. Dr. Bawna Sirohi
3. Dr. Subathra
4. Dr. Rajapriya Ayappan
5. Dr. Ethiraj Balaji Prasadh

TOPICS

1. Breast cancer in young women: Challenges and Outcomes
2. Systemic therapy for breast cancer and fertility preservation
3. Update in radiation treatment for breast cancer
4. Panel discussion with 3 case scenarios

Thank you for spending your valuable time reading this newsletter.

Leaving you with something to think about:

"There should be laughter after pain.
There should be sunshine after rain.
These things have always been the same.....
(So why worry now ?")

Dire Straits - "Why Worry"

SO LET US HELP OUR YOUNG CANCER SURVIVORS TO WALK TOWARDS THE RAY OF HOPE OF PARENTHOOD.

- FPSI Team

The Onco Fertility Journal

Offical publication of the Fertility Preservation Society

Scope of the Journal

The Onco Fertility Journal covers technical and clinical studies related to health, ethical and social issues in the field of Fertility preservation, Protection for cancer patients, women with severe endometriosis, Haematological and Immunological Disease. Articles with clinical interest and implications will be given preference.

Indexing Information

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