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OPINION

Installing oncofertility programs for common cancers in limited resource settings (Repro-Can-OPEN Study): An extrapolation during the global crisis of Coronavirus (COVID-19) pandemic

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Abstract

Purpose The state of limited resource settings that Coronavirus (COVID-19) pandemic has created globally should be taken seriously into account especially in healthcare sector. In oncofertility, patients should receive their fertility preservation treatments urgently even in limited resource settings before initiation of anticancer therapy. Therefore, it is very crucial to learn more about oncofertility practice in limited resource settings such as in developing countries that suffer often from shortage of healthcare services provided to young patients with cancer.

Methods As an extrapolation during the global crisis of COVID-19 pandemic, we surveyed oncofertility centers from 14 developing countries (Egypt, Tunisia, Brazil, Peru, Panama, Mexico, Colombia, Guatemala, Argentina, Chile, Nigeria, South Africa, Saudi Arabia, and India). Survey questionnaire included questions on the availability and degree of utilization of fertility preservation options in case of childhood cancer, breast cancer, and blood cancer.

Results All surveyed centers responded to all questions. Responses and their calculated oncofertility scores showed different domestic standards for oncofertility practice in case of childhood cancer, breast cancer, and blood cancer in the developing countries under limited resource settings.

Conclusions Medical practice in limited resource settings has become a critical topic especially after the global crisis of COVID-19 pandemic. Understanding the resources necessary to provide oncofertility treatments is important until the current COVID-19 pandemic resolves. Lessons learned will be valuable to future potential worldwide disruptions due to infectious diseases or other global crises.

Keywords oncofertility · cancer · limited resource settings · COVID-19 · pandemic

Introduction

Recent advances in cancer diagnosis and treatment over the past four decades have led to a significant increase of the overall survival rates in most cases of young women and men with cancer [1]. Unfortunately, several malignancies occur at young age and necessitate aggressive anticancer therapies including alkylating chemotherapy and ionizing radiation that may lead to gonadotoxicity and future fertility loss as

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devastating side effects. Accordingly, the topic of how to prevent or mitigate the chemotherapy- and radiotherapy-induced gonadotoxicity, and subsequent fertility loss, has gained a growing importance [2–5]. Oncofertility is an interdisciplinary field at the intersection of oncology and reproductive medicine that aims to provide effective fertility options to young cancer patients through several fertility preservation and restoration strategies. The term "oncofertility" was coined in 2006 by the Oncofertility Consortium, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA [6–8].

According to the most recent international guidelines, several established, debatable and experimental oncofertility options can be offered to young female and male patients with cancer in order to preserve and restore their fertility (Table 1) [9–11]. Seldom, if ever, little data is available about oncofertility practice in limited resource settings. The recent Coronavirus (COVID-19) pandemic has resulted in a rapid cascade of unprecedented events around the globe including lockdowns and significant shortage of resources and services. The state of limited resource settings that COVID-19 pandemic has created globally should be taken seriously into account especially in healthcare sector. Thousands of patients worldwide have been affected due to cancelation or postponement of their medical treatments. In oncofertility, patients should receive their fertility preservation treatments urgently even in limited resource settings before initiation of anticancer therapy. Therefore, it is very crucial to learn more about oncofertility practice in limited resource settings such as in developing countries that suffer often from shortage of healthcare services provided to young patients with cancer.

Over the past few years, the Oncofertility Consortium has studied oncofertility practice in developing countries. The Oncofertility Consortium had generated a survey within its Oncofertility Professional Engagement Network (OPEN) [12] (Fig 1) to explore the barriers and opportunities associated with oncofertility practice in 14 developing countries in Africa, Latin America and Asia, including Egypt, Tunisia, Nigeria, South Africa, Brazil, Argentina, Chile, Peru, Panama, Mexico, Colombia, Guatemala, Saudi Arabia, and India. The survey questions were grouped into six categories: country profile, cancer care, fertility treatments, fertility preservation treatments, barriers to oncofertility, and opportunities of oncofertility. Responses from the surveyed centers in the 14 developing countries were collected, reviewed, and discussed. The results of the survey were published in two articles in the *Journal of Global Oncology*, one of the American Society of Clinical Oncology (ASCO) official journals [13, 14]. The surveyed centers from the 14 developing countries continue to experience common challenges such as shortage of healthcare services provided to young patients with cancer, lack of awareness among providers and patients, cultural and religious constraints, lack of insurance coverage, high out-of-pocket costs for patients, and lack of funding to support oncofertility programs. Despite these barriers, many opportunities exist and create a great potential for the future.

The limited resources in developing countries make their proper allocation of utmost necessity particularly in a complex medical field as oncofertility. As a practical approach, the Oncofertility Consortium has designed this new study: the Repro-Can-OPEN: Reproduction and Cancer in the Oncofertility Professional Engagement Network, in order to help bridge the gap between the international oncofertility programs and domestic standards in developing countries. Technically, Repro-Can-OPEN study aims to help developing countries install specific oncofertility programs for common cancers such as childhood cancer, breast cancer, and blood cancer according to their contemporary challenges and opportunities.

Methods

As a kickoff, the Oncofertility Consortium sent the Repro-Can-OPEN study questionnaire via email to the previously surveyed centers and experts in the 14

Table 1 Fertility preservation options for patients undergoing gonadotoxic anticancer therapy

Oncofertility options	Female Patients	Male Patients
Established	. Embryo freezing . Egg freezing . Ovarian tissue freezing and autotransplantation	. Sperm freezing
Debatable	. GnRH analogs and hormonal suppression . Oophoropexy . Gonadal shielding . Fractionated chemotherapy and radiotherapy	. GnRH analogs and hormonal suppression . Gonadal shielding . Fractionated chemotherapy and radiotherapy
Experimental	. In vitro maturation of oocytes and vitrification . Artificial ovary . Stem cells . Neoadjuvant cytoprotective pharmacotherapy . Others	. Testicular tissue freezing and autotransplantation . Stem cells . Neoadjuvant cytoprotective pharmacotherapy . Others

Fig. 1 Merger of American and global networks in to one unified network, the Oncofertility Professional Engagement Network (OPEN).

developing countries (Egypt, Tunisia, Nigeria, South Africa, Brazil, Argentina, Chile, Peru, Panama, Mexico, Colombia, Guatemala, Saudi Arabia, and India) to be proposed for childhood cancer, breast cancer and blood cancer. The Repro-Can-OPEN study questionnaire included questions on the availability of fertility preservation options provided to young female and male patients with cancer and whether these options are always, commonly, occasionally or rarely used (Tables 2, 3, 4 and 5). The responses for childhood cancer, breast cancer, and blood cancer from the surveyed centers and experts in the 14 developing countries were collected, reviewed, and analyzed.

To analyze the collected data, our coauthor Dr. Salama from Northwestern University has developed a new scoring system called 'Oncofertility Score'. The 'Oncofertility Score, is a new diagnostic tool to measure the availability and utilization of an oncofertility option for cancer patients in a treating center, country, or group of countries. It is also a prognostic tool to follow up the development of oncofertility options and strategies provided to cancer patients over time. Oncofertility Score is calculated as a percentile ratio between the actual and maximal points of utilization that an oncofertility option might have (Table 2 & Fig 2). When a fertility preservation option is available and always used for cancer patients, it is given (Yes ++++) that weighs 100 actual points (25 points per each +). When a fertility preservation option is available and commonly used for cancer patients, it is given (Yes +++) that weighs 75 actual points (25 points per each +). When a fertility preservation option is available but occasionally used for cancer patients, it is given (Yes ++) that weighs 50 actual points (25 points per each +). When a fertility preservation option is available but only used in research settings for cancer patients, it is given (Yes +) that weighs 25 actual points (25 points per each +). When a fertility preservation option is not available, it is given (No) that weighs 0 actual points. The maximal points of utilization that an oncofertility option might have is 100 when it is available and always used for cancer patients and is given (Yes ++++), (25 points per each +).

In this study with 14 developing countries, the Oncofertility Score is calculated as a percentile ratio between the total actual points and the total maximal points of utilization that an oncofertility option might have. The total actual points for an oncofertility option equal the sum of actual points for this option in all 14 countries. The total maximal points for an oncofertility option equal 100 points multiplied by 14 (number of countries in this study) resulting in 1400 points (Tables 3, 4, 5).

Results

All surveyed centers and experts from the 14 developing countries (Egypt, Tunisia, Nigeria, South Africa, Brazil, Argentina, Chile, Peru, Panama, Mexico, Colombia, Guatemala, Saudi Arabia, and India) responded to all questions. Responses for childhood cancer, breast cancer, and blood cancer and their calculated oncofertility scores are listed in Tables 3, 4, 5.

The oncofertility scores (%) for options provided to children with cancer in the 14 developing countries were as following; gonadal shielding in case of irradiation (67.85%), fractionation of chemo- and radiotherapy (60.71%), oophoropexy in case of pelvic irradiation (46.42%), GnRH analogs in case of old children (9-14 year) (33.92%), oocyte in vitro maturation (IVM) (28.57%), ovarian tissue freezing (25%), testicular tissue freezing (17.85%), neoadjuvant cytoprotective pharmacotherapy (3.57%), artificial ovary (1.78%), stem cells (1.78%) (Table 3 & Fig 3).

The oncofertility scores (%) for options provided to female patients with breast cancer in the 14 developing countries were as following; gonadal shielding in case of irradiation (62.5%), fractionation of chemo- and radiotherapy (62.5%), egg freezing (58.92%), embryo freezing (55.35%), GnRH analogs (55.35%), IVF/ICSI of frozen oocytes (55.35%), frozen embryo transfer (53.57%), ovarian tissue freezing (28.57%), oocyte in vitro maturation (IVM) (28.57%), autotransplantation of frozen ovarian tissue (19.64%), stem cells (3.57%), artificial ovary (1.78%), neoadjuvant cytoprotective pharmacotherapy (1.78%) (Table 4 & Fig 4).

Table 2 Oncofertility Score calculation

Availability and Utilization of an oncofertility option	Available and always used for cancer patients	Available and commonly used for cancer patients	Available but occasionally used for cancer patients	Available but only used in research settings for cancer patients	Not available
Scale Symbol	++++	+++	++	+	-
Actual Points (AP) (25 points per +)	100	75	50	25	0
Maximal Points (MP) (100 points per ++++)	100	100	100	100	100
Oncofertility Score = AP/MP (%)	100%	75%	50%	25%	0%

The oncofertility scores (%) for options provided to patients with blood cancer in the 14 developing countries were as following; gonadal shielding in case of irradiation (67.85%), sperm freezing (66.07%), fractionation of chemo- and radiotherapy (60.71%), egg freezing (58.92%), embryo freezing (55.35%), oophoropexy in case of pelvic irradiation (46.42%), GnRH analogs (33.92%), oocyte in vitro maturation (IVM) (28.57%), ovarian tissue freezing (25%), testicular tissue freezing (17.85%), neoadjuvant cytoprotective pharmacotherapy (3.57%), artificial ovary (1.78%), stem cells (1.78%) Fig 5.

Discussion

Limited resource settings are not exclusive for developing countries as many other countries around the globe may relatively experience similar limiting conditions as happened recently with COVID-19 pandemic. Therefore, medical practice including oncofertility in limited resource settings has become a critical topic that every nation should take into account. Recently, a joint statement from the Oncofertility Consortium and the Alliance For Fertility Preservation on fertility preservation for patients receiving gonadotoxic therapies during the COVID-19 pandemic has been announced [15]. The announcement came after the recommendations from the American Society for Reproductive Medicine (ASRM's COVID-19 Task Force) was distributed [16], which suggests new IVF cycles should not be initiated at this time. Importantly, this pause in services does not apply to urgent fertility preservation for patients receiving gonadotoxic therapies, but in practicality, loss of general IVF may impact practices' standard operations. While clinicians and leaders in the fertility preservation community remain committed to handling these urgent cases, there are evolving geographic, legal, and practical constraints that may cause interruptions or delays. Understanding the resources necessary to provide this required medical option is important until the current pandemic resolves. Lessons learned will be valuable to future potential worldwide disruptions due to infectious diseases or other global crises.

Our Repro-Can-OPEN study showed different oncofertility domestic standards in developing countries under limited resource settings regarding childhood cancer, breast cancer, and blood cancer. Therefore, we will try here to use the results of our study to tailor and install plausible oncofertility programs for common cancers in limited resource settings in developing countries according to their contemporary challenges and opportunities (Table 6).

Immediately after cancer diagnosis, we recommend early referrals of patients to oncofertility specialists in order to check the anticancer therapy plan and determine the related risk of gonadotoxicity and fertility loss. If the risk of gonadotoxicity and fertility loss is greater than 50%, an effective oncofertility strategy should be offered before, during and after anticancer therapy, after obtaining the informed consent from the patient or the legal guardians of a child. After complete cure from cancer, a new assessment of reproductive functions should be performed. If anticancer therapy induced gonadal dysfunction persists, fertility restoration may be achieved by using stored gametes or gonadal tissue [17–23].

Installing oncofertility programs for childhood cancer in 14 developing countries:

The common forms of childhood cancers that may require aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures are leukemia, central nervous system cancers, and lymphoma. **Before initiation of anticancer therapy**, freezing of prepubertal gonadal tissues (ovarian or testicular tissue) should be encouraged and attempted when

Table 3 Oncofertility Options and Scores (%) for Childhood Cancer in 14 developing countries

Childhood Cancer	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total Actual Points	Oncofertility Score (%)
Developing Countries	**Egypt**	**Tunisia**	**Nigeria**	**South Africa**	**Brazil**	**Argentina**	**Chile**	**Peru**	**Panama**	**Mexico**	**Colombia**	**Guatemala**	**Saudi Arabia**	**India**		
Available fertility preservation options for girls with cancer																
- Ovarian tissue freezing	No	Yes (++)	No	No	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	No	Yes (++)	350	25
- Oophoropexy in case of pelvic irradiation	Yes (++)	Yes (+++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	650	46.42
- Oocyte in vitro maturation (IVM)	No	No	Yes (+)	No	Yes (++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (+)	400	28.57
- Artificial ovary	No	No	No	No	Yes (+)	No	No	No	No	No	No	No	No	No	25	1.78
Available fertility preservation options for boys with cancer																
- Testicular tissue freezing	No	No	Yes (++)	No	Yes (+)	No	No	No	No	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	250	17.85
Available fertility preservation options for both girls and boys with cancer																
- GnRH analogs in case of old child (9-14 year)	No	Yes (++)	No	Yes (++)	Yes (+++)	Yes (+)	Yes (++)	No	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	475	33.92
- Gonadal shielding in case of irradiation	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes(+++)	Yes (+++)	950	67.85
- Fractionation of chemo- and radiotherapy	Yes (+++)	Yes (+++)	Yes(+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	No	Yes (+++)	Yes(+++)	Yes (+++)	850	60.71
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	No	No	No	No	Yes (++)	No	50	3.57
- Stem cells	No	No	No	No	No	No	No	No	No	No	No	No	Yes (+)	No	25	1.78

(++++) Available and always used for cancer patients, (+++) Available and commonly used for cancer patients, (++) Available but occasionally for cancer patients, (+) Available but only used in research setting for cancer patients, (No) Not available.

Table 4 Oncofertility Options and Scores (%) for Breast Cancer in 14 developing countries

Breast Cancer	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total Actual Points	Oncofertility Score (%)
Developing Countries	**Egypt**	**Tunisia**	**Nigeria**	**South Africa**	**Brazil**	**Argentina**	**Chile**	**Peru**	**Panama**	**Mexico**	**Colombia**	**Guatemala**	**Saudi Arabia**	**India**		
Available fertility preservation options before anticancer treatment																
- Embryo freezing	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	775	55.35
- Egg freezing	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	825	58.92
- Ovarian tissue freezing	No	Yes (++)	No	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	No	Yes (++)	400	28.57
- Oocyte in vitro maturation (IVM)	No	No	Yes (+)	No	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (+)	400	28.57
- Artificial ovary	No	No	No	No	Yes (+)	No	No	No	No	No	No	No	No	No	25	1.78
Available fertility preservation options during anticancer treatment																
- GnRH analogs	Yes (++)	Yes (+++)	No	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	775	55.35
- Gonadal shielding in case of irradiation	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	875	62.5
- Fractionation of chemo- and radiotherapy	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	875	62.5
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	Yes (+)	No	No	No	No	No	No	No	Yes (+)	No	25	1.78
Available fertility restoration options after anticancer treatment																
- Frozen embryo transfer	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+++)	750	53.57
- IVF/ICSI of frozen oocytes	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	775	55.35
- Autotransplantation of frozen ovarian tissue	No	Yes (++)	No	No	Yes (+)	Yes (+)	Yes (+)	No	Yes (++)	Yes (++)	No	No	No	Yes (++)	275	19.64
- Stem cells	No	No	No	No	Yes (+)	No	No	No	No	No	No	No	No	No	50	3.57

(++++) Available and always used for cancer patients, (+++) Available and commonly used for cancer patients, (++) Available but occasionally for cancer patients, (+) Available but only used in research setting for cancer patients, (No) Not available.

Table 5 Oncofertility Options and Scores (%) for Blood Cancer in 14 developing countries

Blood Cancer	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total Actual Points	Oncofertility Score (%)
Developing Countries	**Egypt**	**Tunisia**	**Nigeria**	**South Africa**	**Brazil**	**Argentina**	**Chile**	**Peru**	**Panama**	**Mexico**	**Colombia**	**Guatemala**	**Saudi Arabia**	**India**		
Available fertility preservation options for female patients																
- Embryo Freezing	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	775	55.35
- Egg freezing	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	825	58.92
- Ovarian tissue freezing	No	Yes (++)	No	No	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	No	Yes (++)	350	25
- Oophoropexy in case of pelvic irradiation	Yes (++)	Yes (+++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	650	46.42
- Oocyte in vitro maturation (IVM)	No	No	Yes (+)	No	Yes (++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (+)	400	28.57
- Artificial ovary	No	No	No	No	Yes (+)	No	No	No	No	No	No	No	No	No	25	1.78
Available fertility preservation options for male patients																
- Sperm Freezing	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes(+++)	Yes (+++)	925	66.07
- Testicular tissue freezing	No	No	Yes (++)	No	Yes (+)	No	No	No	No	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	250	17.85
Available fertility preservation options for both female and male patients																
- GnRH analogs	No	Yes (++)	No	Yes (++)	Yes (+++)	Yes (+)	Yes (++)	No	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	475	33.92
- Gonadal shielding in case of irradiation	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes(+++)	Yes (+++)	950	67.85
- Fractionation of chemo- and radiotherapy	Yes (+++)	Yes (+++)	Yes(+++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	No	Yes (+++)	Yes(+++)	Yes (+++)	850	60.71
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	No	No	No	No	Yes (++)	No	50	3.57
- Stem cells	No	No	No	No	No	No	No	No	No	No	No	No	Yes (+)	No	25	1.78

(+++) Available and always used for cancer patients, (++) Available and commonly used for cancer patients, (+) Available but occasionally for cancer patients, (+) Available but only used in research setting for cancer patients, (No) Not available.

possible. In vitro maturation and vitrification of gametes (oocytes or spermatozoa) and artificial gonads technology (ovary or testis) are still challenging in children and cannot be relied upon as effective oncofertility options in limited resource settings. Oophoropexy before female pelvis irradiation should be attempted when possible. **During anticancer therapy**, gonadal shielding in case of irradiation and fractionation of chemo- and radiotherapy should be attempted in all cases. GnRH analogs in case of old children (9-14 year) could be attempted while neoadjuvant cytoprotective pharmacotherapy is still very experimental in animal models and not yet reliable as an effective oncofertility option. **After anticancer therapy,** and when the patient becomes an adult and wishes for having children, fertility restoration may be achieved by using stored gametes. Autotransplantation of gonadal tissue can be offered to restore fertility but it should be contraindicated in leukemia due to possible contamination of gonadal tissue with leukemic cells. Stem cells reproductive technology is still very experimental and not yet reliable as an effective oncofertility option (Table 6) [8–10, 16–22].

Installing oncofertility programs for breast cancer in 14 developing countries:

Breast cancer is the most common cancer in women during their reproductive years. Breast cancer may require aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures. Women with BRCA1 or BRCA2 mutations carry significant higher risks to develop breast and ovarian cancers, and they should receive oncofertility care as well. **Before initiation of anticancer therapy**, freezing of embryos or eggs should be attempted in all cases using tamoxifen, letrozole or random-start protocol for controlled ovarian stimulation to avoid high estradiol levels. Freezing of ovarian tissue should be attempted when possible. In vitro maturation and vitrification of oocytes could be attempted however artificial ovary technology is still challenging and cannot be relied upon as an effective oncofertility option in limited resource settings. **During anticancer therapy**, GnRH analogs and fractionation of chemo- and radiotherapy should be attempted in all cases. Gonadal shielding might be needed in case of combined irradiation to ovaries. Neoadjuvant cytoprotective pharmacotherapy is still very experimental in animal models and not yet reliable as an effective oncofertility option. **After anticancer therapy,** fertility restoration may be achieved

Fig. 2 Oncofertility Score calculation

$$\text{Oncofertility Score} = \frac{\text{Actual Points (AP) of utilization that an oncofertility option might have}}{\text{Maximal Points (MP) of utilization that an oncofertility option might have}} \%$$

by frozen embryo transfer, or in vitro fertilization of stored oocytes. Autotransplantation of ovarian tissue can be offered to restore fertility but it should be contraindicated in patients with BRCA mutations due to higher risks of developing ovarian cancer. Stem cells reproductive technology is still very experimental and not yet reliable as an effective oncofertility option (Table 6) [8–10, 16–22].

Installing oncofertility programs for blood cancer in 14 developing countries:

The common forms of blood cancers that occur during the reproductive age and may require immediate aggressive gonadotoxic anticancer therapy and hence necessitate prior fertility preservation measures are acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), Non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL). **Before initiation of anticancer therapy**, freezing of embryos or gametes (oocytes or spermatozoa) should be attempted in all cases. Freezing of gonadal tissues (ovarian or testicular tissue) should be attempted when possible. In vitro maturation and vitrification of gametes could be attempted however artificial gonads technology is still challenging and cannot be relied upon as an effective oncofertility option in limited resource settings. Oophoropexy before female pelvis irradiation should be attempted when possible. **During anticancer therapy**, gonadal shielding in case of irradiation and fractionation of chemo- and radiotherapy should be attempted in all cases. GnRH analogs could be attempted while neoadjuvant cytoprotective pharmacotherapy is still very experimental in animal models and not yet reliable as an effective oncofertility option. **After anticancer therapy,** fertility restoration may be achieved by frozen embryo transfer, or in vitro fertilization of stored gametes. Autotransplantation of gonadal tissue can be offered to restore fertility but it should be contraindicated in leukemia due to possible contamination of gonadal tissue with leukemic cells. Stem cells reproductive technology is still very experimental and not yet reliable as an effective oncofertility option (Table 6) [8–10, 16–22].

After installation of these specific oncofertility programs for common cancers in the 14 developing countries, we encourage all partners to use 'oncofertility score' as a prognostic tool to follow up the development of the new oncofertility

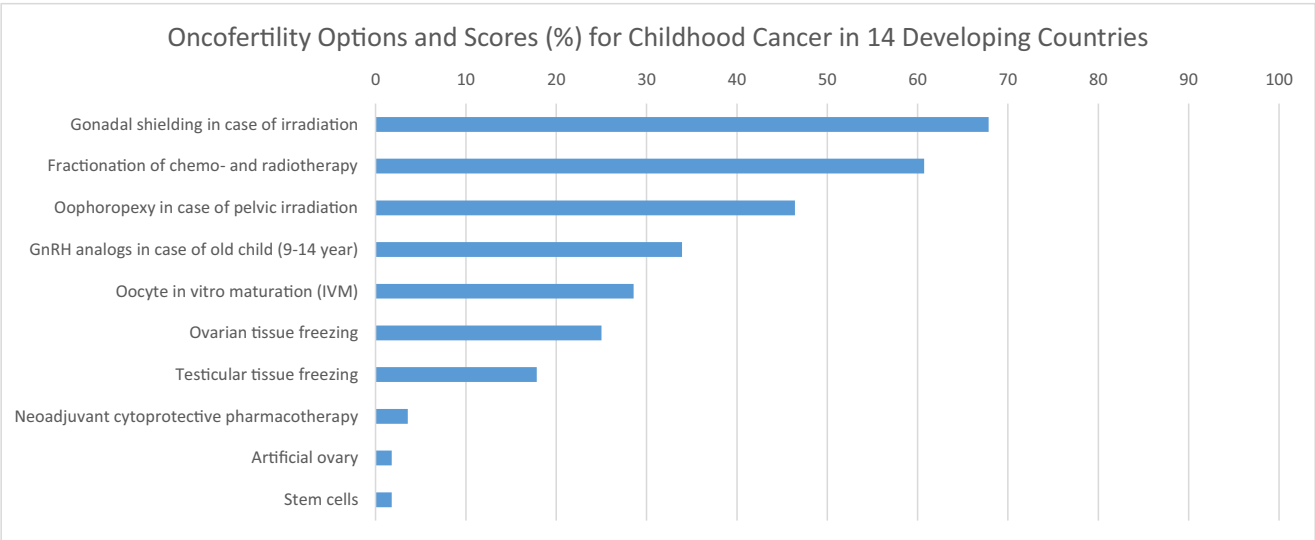

Fig. 3 Oncofertility Options and Scores (%) for Childhood Cancer in 14 developing countries

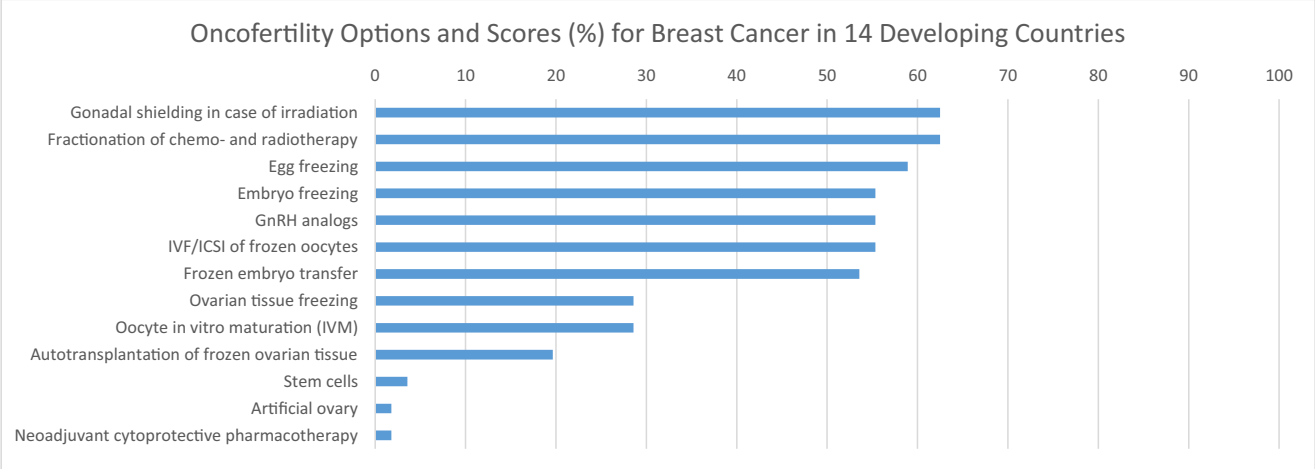

Fig. 4 Oncofertility Options and Scores (%) for Breast Cancer in 14 developing countries

programs and options provided to cancer patients over time. If oncofertility options are rejected, contraindicated, infeasible, unsuccessful or unavailable, adoption and third-party reproduction (sperm, egg, and embryo donation and surrogacy) can be offered as family building alternatives when possible [5].

Conclusion

Medical practice in limited resource settings has become a critical topic that every nation should take into account especially after the global crisis of COVID-19 pandemic. Our Repro-Can-OPEN study showed different oncofertility domestic standards in limited resource settings in developing countries regarding childhood cancer, breast cancer, and blood cancer. Installation of specific oncofertility programs for common cancers such as childhood cancer, breast cancer, and blood cancer in developing countries according to their contemporary challenges and opportunities is highly recommended. Dissemination of this study results and recommendations will provide efficient oncofertility edification and modelling to pediatric, breast and hemato-oncologists in developing countries and help them offer the best care possible to their socio-economically disadvantaged patients. Meanwhile, the Oncofertility Consortium will continue to engage more stakeholders in developing countries to use the powerful networks in the United States and other developed countries to help build a sustainable oncofertility core competency worldwide.

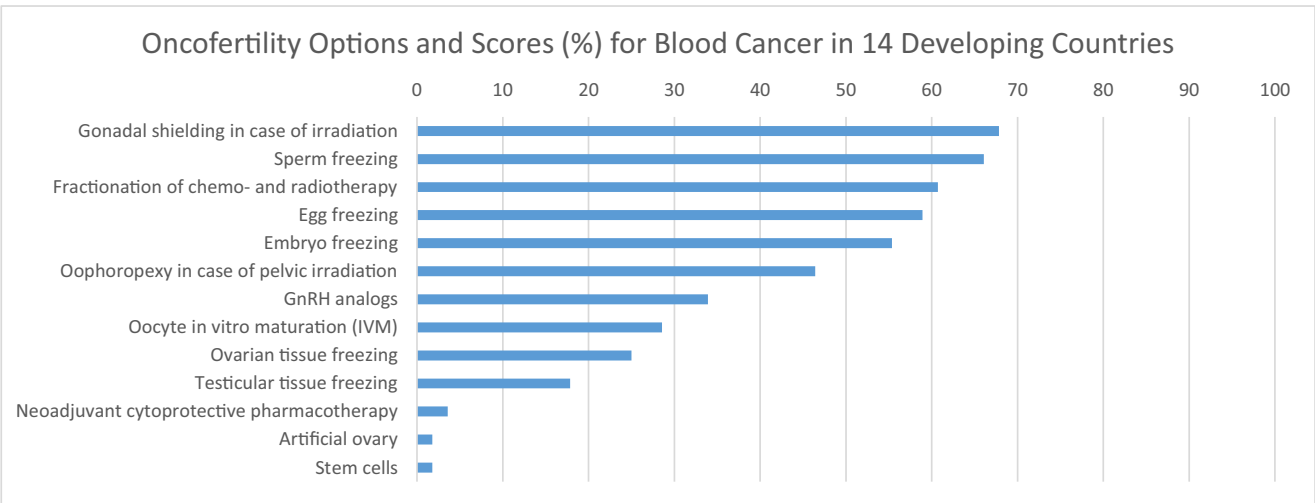

Fig. 5 Oncofertility Options and Scores (%) for Blood Cancer in 14 developing countries

Table 6 Plausible fertility preservation and restoration strategies for cancer patients in 14 developing countries

Cancer Patients	Before Anticancer therapy (Fertility Preservation)	During Anticancer therapy (Fertility Preservation)	After Anticancer therapy (Fertility Restoration)
Childhood Cancer Leukemias, central nervous system cancers, and lymphoma	. Freezing of gonadal tissue . In vitro maturation and vitrification of gametes (not yet reliable in children) . Oophoropexy in case of female pelvic radiation . Artificial gonads technology (not yet reliable)	. Gonadal shielding . Fractionation of chemo- and radiotherapy . GnRH analogs in case of old child (9-14 year) . Neoadjuvant cytoprotective pharmacotherapy (not yet reliable)	. IVF/ICSI of frozen gametes . Autotransplantation of frozen gonadal tissue (contraindicated in leukemia) . Stem cells (not yet reliable)
Breast Cancer Patients with or without BRCA mutations	. Egg freezing . Embryo freezing . Ovarian tissue freezing . In vitro maturation (IVM) of oocytes and vitrification . Artificial ovary technology (not yet reliable)	. GnRH analogs . Fractionation of chemo- and radiotherapy . Gonadal shielding . Neoadjuvant cytoprotective pharmacotherapy (not yet reliable)	. Intrauterine transfer of frozen embryo . IVF/ICSI of frozen oocytes . Autotransplantation of frozen ovarian tissue (contraindicated in BRCA mutations) . Stem cells (not yet reliable)
Blood Cancer Leukemia (ALL, AML), and Lymphoma (NHL, HL)	. Freezing of gametes . Freezing of gonadal tissue . In vitro maturation and vitrification of gametes . Oophoropexy in case of female pelvic radiation . Artificial gonads technology (not yet reliable)	. GnRH analogs . Gonadal shielding . Fractionation of chemo- and radiotherapy . Neoadjuvant cytoprotective pharmacotherapy (not yet reliable)	. Intrauterine transfer of frozen embryo . IVF/ICSI of frozen gametes . Autotransplantation of frozen gonadal tissue (contraindicated in leukemia) . Stem cells (not yet reliable)

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