Supplementary Material - 1

Salama M, Ataman L, Taha T, et al. Building Oncofertility Core Competency in Developing Countries: Experience from Egypt, Tunisia, Brazil, Peru, and Panama. J Glob Oncol. 2018;4:1-11.

Table 1: Developing Country's Profile

	Egypt	Tunisia	Brazil	Peru	Panama
Area (million km^2)	1	0.16	8.5	1.28	0.07
Location	Africa	Africa	South America	South America	Central America
Language	Arabic	Arabic	Portuguese	Spanish	Spanish
Population (million)	92	11	206	31	3.4
Fertility rate (births per woman)	2.8	1.98	1.9	2.26	2.4
Religion	90% Muslims 9% Christians 1% others	99 % Muslims 1% Christians and Jewish	65% Catholic 22% Protestant 8% No Religion 5% Others	80% Catholics 20% others	74% Catholics 19% Protestants 7% other
Culture	Conservative	Conservative	Eclectic and syncretic	Conservative	Conservative
Economy	Lower-middle income country	Lower-middle income country	Upper-middle-income country	Upper-middle income country	Upper-middle income country
Nominal GDP Total (billion USD)	330	43.6	2469	189	52
Nominal GDP Per Capita (thousand USD)	3740	3922	11979	5700	13268
Global Competitiveness Index (GCI)	116	92	75	67	50
Health system world ranking in GCI	86	52	69	98	55
Life expectancy in years (Females)	73	77.8	79	77	81
Life expectancy in years (Males)	69	73	71	72	75
Total Expenditure on Health as % of GDP	5%	7%	10%	5%	8%
Expenditure on Health (Sources)	72% out-of-pocket 25% state 3% others	37% from Tunisian households, 35% from CNAM 28% directly from the government	52% out-of-pocket 48% state	35% out-of-pocket 30% contribution of employers (tax expenses) 31% state 4% others	73.2% state 22.3% out-of-pocket 4.5% other
State's Health Insurance	Covers 40% of populations	Covers 80% of populations	Covers 100% of population	Covers 62% of population	Covers 37% of population

Table 2: Cancer Care

	Egypt	Tunisia	Brazil	Peru	Panama
Cancer incidence rate (per 100,000)	166	116	291	150	147.9
Cancer mortality rate (per 100,000)	95	66.7	92	92	70.6
Common cancers in women (%)	Breast (32%), liver (13%), brain (5%), ovary (4%), Non-Hodgkin lymphoma (4%), and thyroid (3%).	Breast (31.9%), skin (5.7%), colon (5.7%), cervix (4.3%), ovary (4.1%), and Non-Hodgkin's lymphoma (3.7%)	Breast (28%), colon and rectum (9%), uterine cervix (8%), lung and respiratory system (5%), and stomach (4%).	Cervix (24%), Breast (17%), Stomach (9%) and Skin (6%)	Breast (36.6%), Cervix (26.6%), Colon (13.4%), Stomach (10.4%), Lung (6.8%), Ovary (6.2%).
Common cancers in men (%)	Liver (33%), bladder (10%), lung (6%), Non-Hodgkin lymphoma (5%), brain (5%), and prostate (4%).	Lung (22.9%), bladder (9.9%), prostate (8.9%), skin (5.9%), colon (5.3%), and stomach (4.5%)	Prostate (29%), lung and respiratory system (8%), colon and rectum (8%), stomach (6%), and mouth (5%).	Prostate (15%), Stomach (15%), Skin (8%), Hematopoietic system (7%) and Lung (6%)	Prostate (54.7%), Stomach (13.3%), Lung (11.3%), Colon (11.1%), Oral (4%), Liver (3.5%), Esophageal (2.1%)
Cancer treatments providers and coverage	- National cancer institutes, university hospitals, specialized cancer hospitals and public hospitals provide for free services or are covered by insurance. - Some major private hospitals provide cancer treatments covered by insurance or out-of-pocket payment.	The National Cancer Institute of Salah Azaiz covers 25% of cases, other patients diagnosed with cancer are cared for either in the university hospitals of Sousse and Sfax or in private structures. Cancer treatment provide from 50% of households, 35% of the government, and 15% of the CNAM	- Cancer institutes, university hospitals and specialized public hospitals provide services covered by the national public health system. - Private hospitals provide cancer treatments covered by private insurance or out-of-pocket payment.	- Coverage of cancer treatments are possible through FISSAL (Fondo Intangible Solidario de Salud) and an integrated health system (SIS, Sistema Integral de Salud). - Cancer treatment providers include The National cancer institute (INEN), public hospitals and private specialized cancer clinics.	- National Institute of Oncology is a large public hospital providing mostly for free and public health insurance services. - Large public hospitals also provide some cancer treatments for insured and uninsured patients. - Private hospitals and private providers, private health insurance or out-of-pocket costs.
National cancer registry	Under development	3 cancer registry: registry of the north-Tunisia; registry of center region and registry of south Tunisia.	Fully implemented	Under development	The Gorgas Memorial Institute for Health Studies/ Geographic Information System of Incidence and Mortality by Cancer.

Table 3: Fertility Treatments

		Egypt	Tunisia	Brazil	Peru	Panama
Who can receive fertility treatments?		Married heterosexual couples only	Married heterosexual couples only	Married/Stable union heterosexual and homosexual couples, Single women.	Married/unmarried couples/persons	Unregulated, provider dependent
Assisted Reproductive Techniques (ART)	IUI	Available	Available	Available	Available	Available
	IVF	Available	Available	Available	Available	Available
	ICSI	Available	Available	Available	Available	Available
	PGD	Available	Not available	Available	Available	Available
	Sex Selection	Available	Not available	Available	Not available	Available
Cryo-preservation	Embryo Freezing	Available	Available	Available	Available	Available
	Egg Freezing	Available	Available	Available	Available	Available
	Social egg freezing	Not available	Not available	Available	Not available	Available
	Ovarian tissue freezing	Not available	Will be available in 3 months	Available, under research projects	Recently available	Available
	Sperm freezing	Available	Available	Available	Available	Available
	Testicular tissue freezing	Not available	Not available	Available, under research projects	Not available	Available
Third Party Reproduction	Sperm donation	Prohibited	Prohibited	Allowed	Available but unregulated	Available but unregulated
	Egg donation	Prohibited	Prohibited	Allowed	Available but unregulated	Available but unregulated
	Embryo donation	Prohibited	Prohibited	Allowed	Available but unregulated	Available but unregulated
	Surrogacy	Prohibited	Prohibited	Allowed	Available but unregulated	Available but unregulated
Adoption		Prohibited	Allowed	Allowed	Allowed	Allowed
Insurance coverage for fertility treatments		No	Fertility treatments are covered by the CNAM, which fully supports 3 stimulation cycles in women under the age of 40 and who have no children.	Yes, but pretty recent. Majority of them no cover	No	No
Fertility treatments providers		80% private centers 20% public hospitals	The centers of assisted medical procreation can do about 9000 IVF cycle/year, 1800 of which are provided in public centers	93% private centers 7% public hospitals	Mostly private centers, only one public hospital	90% private centers 10% public hospitals
Average cost of a single cycle of IVF/ICSI (USD)		500 - 1000	800 - 1500	1500 - 5000	3500 - 5000	2500 - 5000
National registry		Not available	Not available	Available	Not available (but we have Regional Registry for Latin America).	Not available

Table 4: Fertility Preservation Treatments

		Egypt	Tunisia	Brazil	Peru	Panama
Who can receive fertility preservation treatments?		Married heterosexual couples more than cancer patients.	Patients diagnosed with a cancer	Married/Stable union heterosexual and homosexual couples, Single women, cancer patients.	Married/unmarried couples/persons, more than cancer patients.	Unregulated, provider dependent
Cryo-preservation	Embryo Freezing	Available	Available	Available	Available	Available
	Egg Freezing	Available	Available	Available	Available	Available
	Social egg freezing	Not available	Not available	Available	Not available	Available
	Ovarian tissue freezing	Not available	Will be available in 3 months	Available, under research projects	Recently available	Available
	Sperm freezing	Available	Available	Available	Available	Available
	Testicular tissue freezing	Not available	Not available	Available, under research projects	Not available	Available
Insurance coverage for fertility preservation treatments		No	No	Yes, but pretty recent. Majority of them no cover	No	No
Fertility preservation treatments providers		80% private centers 20% public hospitals	100% public hospitals	93% private centers 7% public hospitals	Private centers	100% private centers
Average cost of a single frozen cycle of IVF/ICSI (USD)		500 - 1000	800 - 1500	2000 - 5500	3500 - 5000	1500 - 3500
National registry		Not available	Not available	Available (not fully implemented - don`t consider cancer patients alone).	Not available	Not available

Table 5: Barriers to Oncofertility

	Egypt	Tunisia	Brazil	Peru	Panama
1- Medical Barriers					
Lack of awareness among oncologists, gynecologists & patients	Yes	Yes	Yes	Yes	Yes
Lack of advances in early diagnosis and treatment of cancer	Yes	Yes	No	Yes	Yes
Lack of inter-institutional communications	Yes	Yes	Yes	Yes	Yes
Lack of referrals from oncologists	Yes	Yes	Yes	Yes	Yes
Lack of some fertility preservation options	Yes	Yes	Yes	Yes	No
Lack of oncofertility specialists	Yes	Yes	No	Yes	No
2- Economic Barriers					
Lack of health insurance coverage for fertility services	Yes	Yes	Yes. Coverage pretty recent. Few insurance companies.	Yes	Yes
Most of fertility services are provided in private centers	Yes	NO	Yes	Yes	Yes
Lack of institution and research fund	Yes	Yes	Yes	Yes	Yes
3- Social Barriers					
Sperm donation	Not accepted	Not accepted	Accepted	Not accepted	Accepted
Egg donation	Not accepted	Not accepted	Accepted	Not accepted	Accepted
Embryo donation	Not accepted	Not accepted	Accepted	Not accepted	Accepted
Surrogacy	Not accepted	Not accepted	Accepted	Not accepted	Not Accepted
Adoption	Accepted	Accepted	Accepted	Accepted	Accepted
4- Legal Barriers					
Sperm donation	Prohibited	Prohibited	Allowed	Unregulated	Unregulated
Egg donation	Prohibited	Prohibited	Allowed	Unregulated	Unregulated
Embryo donation	Prohibited	Prohibited	Allowed	Unregulated	Unregulated
Surrogacy	Prohibited	Prohibited	Allowed	Unregulated	Unregulated
Adoption	Prohibited	Allowed	Allowed	Allowed	Allowed

Table 6: Opportunities to Oncofertility

	Egypt	Tunisia	Brazil	Peru	Panama
Chances to overcome medical barriers	Yes	Yes	Yes	Yes	Yes
Chances to overcome economic barriers	Yes	Yes	Yes	Yes	Yes
Chances to overcome social barriers	No	No	Yes	Yes	Yes
Chances to overcome legal barriers	No	No	Yes	Yes	No

Supplementary Material - 2

Salama M, Ataman-Millhouse L, Sobral F, et al. Barriers and Opportunities of Oncofertility Practice in Nine Developing Countries and the Emerging Oncofertility Professional Engagement Network. J Glob Oncol. 2018;4:1-7.

Table 1: Country's Profile 2016/2017 according to Human Development Reports – United Nations (UN) http://hdr.undp.org/en/countries

	Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
Area (million km^2)	1.96	1.14	0.1	2.78	0.756	0.924	1.22	2.15	3.28
Location	North America	South America	Central America	South America	South America	Africa	Africa	Asia	Asia
Language	Spanish	Spanish	Spanish	Spanish	Spanish	English (Official)	11 official languages	Arabic	Hindi
Population (million)	127	48.2	16.58	43.85	17.9	182.2	54	32.28	1320
Fertility rate (births per woman)	2.2	1.9	3	2.31	1.8	5.42	2.34	2.71	2.5
Religion (%)	89.3% Catholics 8% Protestants	87% Catholics 11.5% Protestants	45% Catholics 42% Protestants 11% None/Atheist/Agnostic 2% Others	66% Catholics 9% Protestants 21% No religion 3% Others	55% Catholics 13% Protestants 25% No religion	49.3% Christians 48.8% Muslims 1.9% Others	86% Christians 1.5% Muslims 1.2 % Hindu 0.3% Jews	100% Muslims	80% Hindu 14% Muslims 2% Christians 4% Others
Culture	Conservative	Conservative	Conservative	Eclectic	Conservative	Conservative	Multicultural	Conservative	Conservative
Economy	Upper middle income country	Upper middle income country	Lower middle income country	Upper middle income country	High	Lower middle income country	Upper middle income country	Upper income country	Lower middle income country
Nominal GDP Total (billion USD)	1047	282	69	644	250	494	680	689	2848
Nominal GDP Per Capita (USD)	8208	5805	4146	14686	15793	2763	12390	21100	2134
Human Development Index (HDI) rank	77	95	125	45	38	152	119	38	131
Life expectancy in years (Females)	79.4	77.8	76.3	79	84.7	56	66.7	75.9	69.9
Life expectancy in years (Males)	74.6	70.7	69.9	73	79	53	61.2	73.2	66.9
Public health expenditure (% of GDP)	3.3	5.4	2.3	2.7	3.9	0.9	4.2	4.7	1.4
Total Expenditure on Health (Resources %): State, Private, Out of pocket & Others	52% State 6% Private 41% Out of pocket 1% Others	67% State 11% Private 18% Out of pocket 4% Others	32% State 14% Private 52% Out of pocket 2% Others	43% State 19% Private 38% Others	60% State 39% Out of pocket 1% Others	23.9% State 69.35% Out of pocket 6.75% Others	49.2% State 48.2% Private 2.6% Others	74.5% State 25.5% Out of pocket	30% State 70% Out of pocket
Health Insurance Coverage for population (%)	82%	96.7%	96%	100%	100%	5%	20%	100%	29%

Table 2: Cancer Care – WHO GLOBOCAN 2012 http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

	Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
Cancer incidence rate in both sexes (per 100,000)	131.5	160.6	130.4	216.7	175.7	100.1	187.1	91.1	94
Cancer mortality rate in both sexes (per 100,000)	68.9	85	96.4	115.1	103	72.1	117.9	53.9	64.5
Common cancers in women (%) (*)	Breast (24.8%), Cervical (16.9%), Colorectal (4.8%), Stomach (4.3%), Liver (4%)	Breast (23.4%), Cervical (12.6%), Colorectal (8.2%), Stomach (6%), Thyroid (5.8%)	Cervical (17.9%), Stomach (15.6%), Liver (10.5%), Endometrial (10.4%), Breast (8.1%)	Breast (32.2%), Colorectal (10.5%), Cervix (8.2%), Lung (5.9%), Ovary (3.8%)	Breast (20.4%), Colorectal (9.6%), Gallbladder (8.0%), Cervix (7.2%), Lung (6.7%).	Breast (42.2%), Cervix (21.8%), Liver (6.4%), Colorectal (3.1%), Non-Hodgkin lymphoma (2.7%).	Breast (24.5%), Cervix (19.3%), Lung (6.4%), Colorectal (5.4%), Esophagus (4%)	Breast (30%), Colorectal (9.5%), Thyroid (9.1%), Non-Hodgkin lymphoma (5.7%), Uterine (4.7%)	Breast (27%), Cervical (22.9%), Colorectal (5.1%), Ovary (5%), Oral (4.3%)
Common cancers in men (%) (**)	Prostate (21.4%), Lung (8.3%), Colorectal (7.1%), Stomach (6.3%), Leukemia (5.1%)	Prostate (27.8%), Stomach (10.7%), Lung (8.8%), Colorectal (7.7%), Non-Hodgkin lymphoma (5.4%)	Stomach (19.9%), Prostate (17.7%), Liver (13.2%), Lung (6.7%), Leukemia (5.7%)	Prostate (20.4%), Lung (14%), Colorectal (13.2%), Bladder (4.9%), Kidney (4.8%)	Prostate (27.9%), Stomach (12%), Lung (8.8%), Colorectal (8.2%), Kidney (3.9%)	Prostrate (32%), Liver (21.1%), Non-Hodgkin lymphoma (6.2%), Colorectal (5.8%), Pancreas (2.5%)	Prostate (26.6%), Lung (12.6%), Colorectal (6.7%), Esophagus (6.1%), Kaposi sarcoma (4.5%)	Colorectal (14.2%), Non-Hodgkin lymphoma (8.7%), Prostate (8.5%), Lung (7.4%), Liver (6.2%)	Oral (11.3%), Lung (11.3%), Stomach (9.1%), Colorectal (7.7%), Other pharynx (6.6%)
Cancer treatments providers and coverage	- Social security as Mexican Social Security Institute (IMSS) or Institute of Safety and Social Services for Government Workers (ISSSTE) provides free service and treatment - Seguro popular provides treatment to uninsured people to specific cancers as breast, testis, prostate, colorectal, cervical, ovarian, lymphoma and all childhood neoplasms - Private hospitals and private providers, private health insurance or out-of-pocket costs.	- All services for cancer care are available in the Colombian health care system - Health insurance institution (EPS) provides cancer treatment through high-Cost Diseases Office - The majority of cancer treatments are part of the obligatory health plan	- Guatemalan Social Security Institute (IGSS) provides free service and treatment. - Large public hospitals also provides some service and cancer treatments. - National Cancer Institute provide cancer treatments - Private hospitals and private providers, private health insurance or out-of-pocket costs.	- Cancer institutes, university hospitals and specialized public hospitals provide services covered by the national public health system. - Private hospitals provide cancer treatments covered by private insurance or out-of-pocket payment.	- Cancer institutes, university hospitals and specialized public hospitals provide services covered by the national public health system. - Private hospitals provide cancer treatments covered by private insurance or out-of-pocket payment.	- A few large teaching hospitals provide care and Private hospitals and private providers, private health insurance or out-of-pocket costs.	- 80% State funded - 20% Private funded with varying levels of access to treatment depending on option funded.	- Many government and private hospitals.	- Regional Cancer centers; University hospitals; Public Hospitals; Specialized cancer centers.
National cancer registry	Under development	Fully implemented	Under development	Fully implemented	Fully implemented	Under Development	Fully implemented	Fully implemented	Fully implemented

(*) The most common cancers in young women and girls that may require aggressive gonadotoxic anticancer treatments and necessitate prior fertility preservation measures are breast, cervix, leukemia, lymphoma, central nervous system, renal, and bone cancers.
(**) The most common cancers in young men and boys that may require aggressive gonadotoxic anticancer treatments and necessitate prior fertility preservation measures are testicular cancer, leukemia and lymphoma and central nervous system cancers.
American Society of Clinical Oncology recommendations on fertility preservation in cancer patients

Table 3: Fertility Treatments

		Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
Who can receive fertility treatments?		Unregulated, provider dependent	Unregulated, provider dependent	Unregulated, provider dependent	Married/Stable union heterosexual and homosexual couples, Single women	Unregulated, provider dependent	Heterosexual partners	Married/Stable union heterosexual and homosexual couples, Single women	Married heterosexual couples only	Married heterosexual couples
Assisted Reproductive Techniques (ART)	IUI	Available	Available	Available	Available	Available	Available	Available	Available	Available
	IVF	Available	Available	Available	Available	Available	Available	Available	Available	Available
	ICSI	Available	Available	Available	Available	Available	Available	Available	Available	Available
	PGD	Available	Available	Available	Available	Available	Available	Available	Available	Available
	Sex Selection	Not available	Not available	Not available	Available only for medical reasons	Available	Available	Available	Available	Prohibited
Cryo-preservation	Embryo Freezing	Available	Available	Available	Available	Available	Available	Available	Available	Available
	Egg Freezing	Available	Available	Available	Available	Available	Available	Available	Available	Available
	Social egg freezing	Not available	Not available	Not available	Available	Available	Available	Available	Not Available	Available
	Ovarian tissue freezing	Not available	Available	Not available	Recently Available	Available	Not available	Not available	Not Available	Available
	Sperm freezing	Available	Available	Available	Available	Available	Available	Available	Available	Available
	Testicular tissue freezing	Available	Available	Not available	Not Available	Available	Available	Not available	Available	Available
Third Party Reproduction	Sperm donation	Available but unregulated	Available but unregulated	Available	Allowed	Available but unregulated	Available but unregulated	Allowed	Prohibited	Available
	Egg donation	Available but unregulated	Available but unregulated	Available	Allowed	Available but unregulated	Available but unregulated	Allowed	Prohibited	Available
	Embryo donation	Available but unregulated	Available but unregulated	Not available	Allowed	Available but unregulated	Available but unregulated	Allowed	Prohibited	Available
	Surrogacy	Available in one state	Available but unregulated	Available	Not Allowed (only under litigation)	Not available but not illegal	Available but unregulated	Allowed	Prohibited	Available for Indians only
Adoption		Allowed	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed	Available	Available
Insurance coverage for fertility treatments		No	No	No	Yes	Only in some University and public hospitals	No	Less than 1%	No	No
Fertility treatments providers: Private centers (*) Public hospitals (**)		100% Private centers	100% Private centers	100% Private centers	90 % Private centers 10 % Public Hospitals	85% Private centers 15% Public hospitals	80% Private centers 20% Public hospitals	85% Private centers 15% Public hospitals	70% Private centers 30% Public hospitals	99% Private centers 1% Public hospitals
Average cost of a single cycle of IVF/ICSI (USD)		6000	7120	7500	2000 - 3500	5000 - 10000	2000 - 5500	2500 - 6000	4000 - 7000	1500 - 3000
National registry		Not available	Not available	Not available	Available	Available	Not available	Available	Not available	Available

IUI: Intrauterine Insemination, IVF: In Vitro Fertilization, ICSI: Intracytoplasmic Sperm Injection, PGD: Preimplantation Genetic Diagnosis.
(*) Private centers include private hospitals and clinics.
(**) Public hospitals include University and governmental hospitals.

Table 4: Fertility Preservation Treatments

		Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
Who can receive fertility preservation treatments?		Unregulated, provider dependent	Unregulated, provider dependent	Unregulated, provider dependent	Married/Stable union heterosexual and homosexual couples, Single women, cancer patients.	Unregulated, provider dependent	Married /Unmarried	Married/Stable union heterosexual and homosexual couples, Single women, cancer patients.	Married heterosexual couples only	Married/unmarried couples/persons, cancer patients
Cryo-preservation	Embryo Freezing	Available	Available	Available	Available	Available	Available	available	Available	Available
	Egg Freezing	Available	Available	Available	Available	Available	Available	available	Available	Available
	Social egg freezing	Not available	Not available	Not available	Available	Available	Available	available	Not Available	Available
	Ovarian tissue freezing	Not available	Available	Not available	Recently Available	Available	Not available	Not available	Not Available	Available
	Sperm freezing	Available	Available	Available	Available	Available	Available	available	Available	Available
	Testicular tissue freezing	Available	Available	Not available	Not Available	Available	Available	Not available	Available	Available
Insurance coverage for fertility preservation treatments		No	No	No	Only oncology preservation	Only for sperm freezing in testicular cancer	No	Limited to one medical scheme	No	No
Fertility preservation treatments providers: Private centers (*) Public hospitals (**)		100% Private centers	100% Private centers	100% Private centers	90 % Private centers 10 % Public Hospitals	85% Private centers 15% Public hospitals	80% Private centers 20% Public hospitals	85% Private centers 15% Public hospitals	70% Private centers 30% Public hospitals	99% Private centers 1% Public hospitals
Average cost of a single frozen cycle of IVF/ICSI (USD)		10000	11400	13500	2500 - 4000	5000 - 10000	1500	1700 - 5500	800 - 1300	1500 - 3000
National registry		Not available	Not available	Not available	Available	Not available	Not available	Available	Not available	Not available

(*) Private centers include private hospitals and clinics.
(**) Public hospitals include University and governmental hospitals.

Table 5: Barriers to Oncofertility

	Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
1- Medical Barriers									
Lack of awareness among oncologists, gynecologists & patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lack of advances in early diagnosis and treatment of cancer	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Lack of inter-institutional communications	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lack of referrals from oncologists	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lack of some fertility preservation options	No	No	Yes	No	No	Yes	Yes	Yes	Yes
Lack of oncofertility specialists	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
2- Economic Barriers									
Lack of health insurance coverage for fertility services	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Most of fertility services are provided in private centers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lack of institution and research fund	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	With exceptions
3- Social Barriers									
Sperm donation	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Not accepted	Accepted
Egg donation	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Not accepted	Accepted
Embryo donation	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Not accepted	Accepted
Surrogacy	Accepted	Accepted	Accepted	Not accepted	Not accepted	Accepted	Accepted	Not accepted	Accepted
Adoption	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted
4- Legal Barriers									
Sperm donation	Allowed	Unregulated	Unregulated	Accepted	Unregulated	Unregulated	Allowed	Prohibited	Allowed
Egg donation	Allowed	Unregulated	Unregulated	Accepted	Unregulated	Unregulated	Allowed	Prohibited	Allowed
Embryo donation	Allowed	Unregulated	Unregulated	Accepted	Unregulated	Unregulated	Allowed	Prohibited	Allowed
Surrogacy	Allowed only in one state	Unregulated	Unregulated	Working with legislators to be approved	Unregulated	Unregulated	Allowed	Prohibited	Allowed only for Indians
Adoption	Allowed	Allowed	Allowed	Accepted	Allowed	Allowed	Allowed	Allowed	Allowed

Table 6: Opportunities to Oncofertility

	Mexico	Colombia	Guatemala	Argentina	Chile	Nigeria	South Africa	Saudi Arabia	India
Chances to overcome medical barriers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chances to overcome economic barriers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chances to overcome social barriers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Chances to overcome legal barriers	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes

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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.

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

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.

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

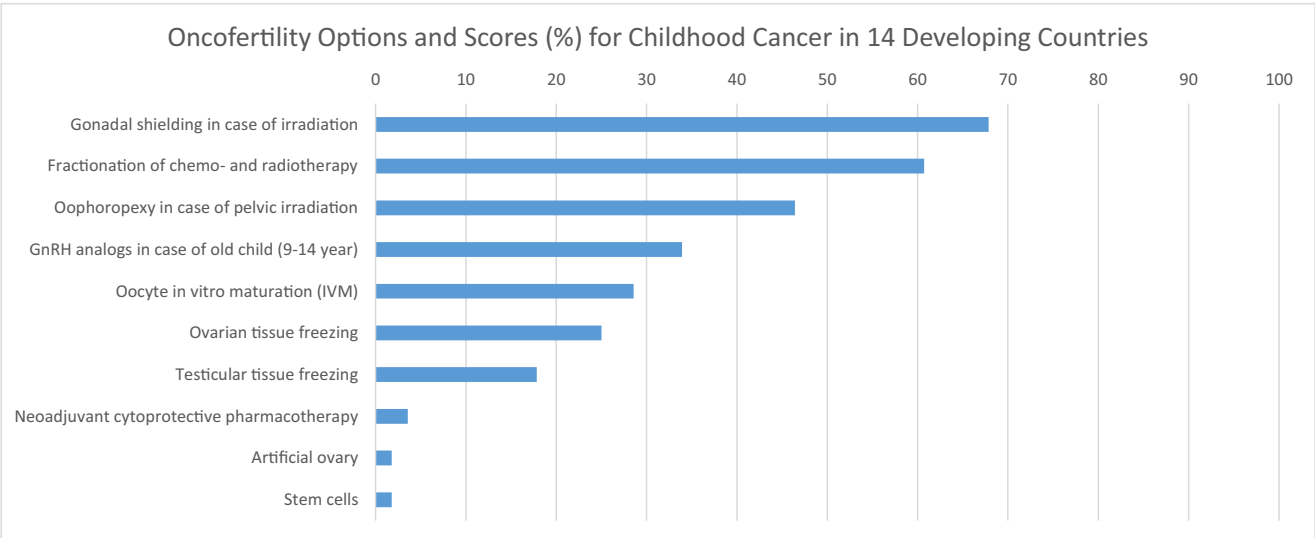

Fig. 3 Oncofertility Options and Scores (%) for Childhood Cancer in 14 developing countries

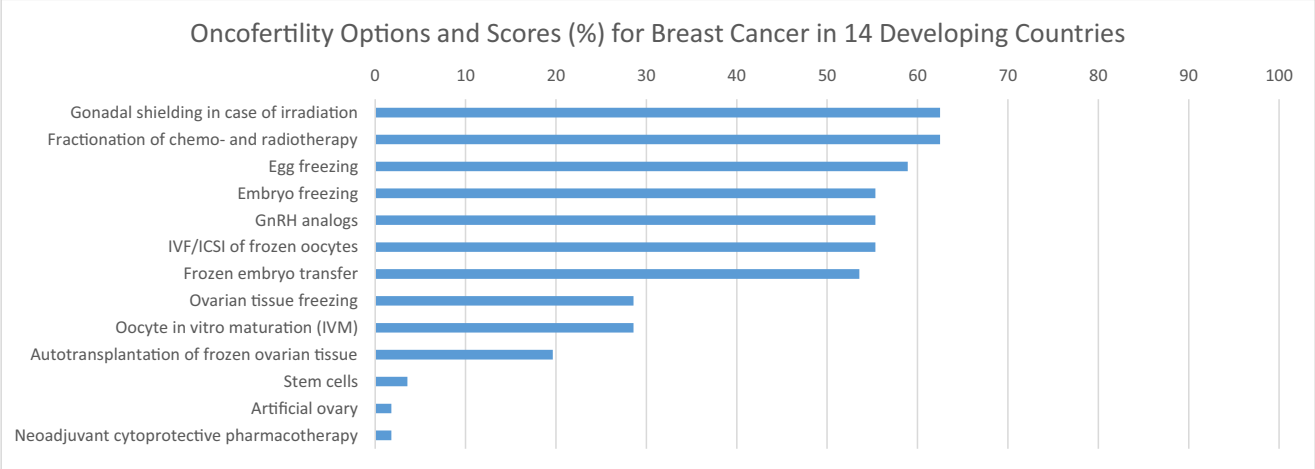

Fig. 4 Oncofertility Options and Scores (%) for Breast Cancer in 14 developing countries

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.

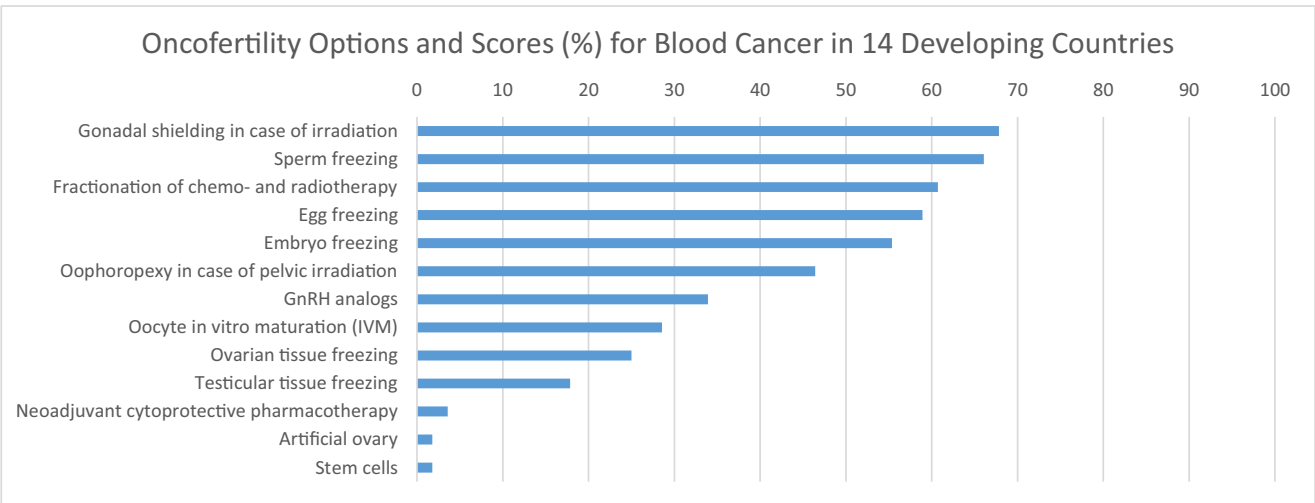

Fig. 5 Oncofertility Options and Scores (%) for Blood Cancer in 14 developing countries

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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FERTILITY PRESERVATION

Installing oncofertility programs for common cancers in optimum resource settings (Repro-Can-OPEN Study Part II): a committee opinion

Practice Committee of the Oncofertility Consortium[1]

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Abstract

Purpose The main objective of Repro-Can-OPEN Study Part 2 is to learn more about oncofertility practices in optimum resource settings to provide a roadmap to establish oncofertility best practice models.

Methods As an extrapolation for oncofertility best practice models in optimum resource settings, we surveyed 25 leading and well-resourced oncofertility centers and institutions from the USA, Europe, Australia, and Japan. The survey 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 three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy; (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM); and (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cell reproductive technology as they are still in preclinical or early clinical research settings. Proper technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients.

Conclusions Our Repro-Can-OPEN Study Part 2 proposed installing specific oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models. This will provide efficient oncofertility edification and modeling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients.

Keywords Oncofertility · Cancer · Optimum resource settings · Best practice · Childhood cancer · Breast cancer · Leukemia · Lymphoma

Introduction

Several malignancies occur at a young age and may necessitate aggressive anticancer therapies including alkylating chemotherapy and ionizing radiation that could lead to gonadotoxicity and subsequent fertility loss as a devastating side effect. According to the most recent international guidelines of the American Society of Clinical Oncology (ASCO) and the American Society for Reproductive Medicine (ASRM), several established, debatable, and experimental oncofertility options can be offered to young female and male patients with cancer to preserve and restore fertility [1, 2]. Established oncofertility options include sperm freezing, embryo freezing, egg freezing, and recently ovarian tissue freezing and autotransplantation. Debatable oncofertility options include GnRH analogs and hormonal suppression, oophoropexy, gonadal shielding, and fractionation of chemotherapy and radiotherapy. Experimental oncofertility options include oocytes in vitro maturation (IVM), artificial ovary, testicular tissue freezing and autotransplantation, in vitro spermatogenesis, neoadjuvant cytoprotective pharmacotherapy, and stem cell reproductive technology.

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However, such oncofertility international guidelines face several challenges in practice. Over the past years, the Oncofertility Consortium has studied oncofertility practice in many countries within its Oncofertility Professional Engagement Network (OPEN). Our previous studies identified a variety of standards in oncofertility practice around the globe due to limited resource settings, shortage of reproductive care 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 [3–9]. Despite these challenges, many opportunities exist and create a significant potential for the future including improved cancer survival rates and improved success rates of many oncofertility options as well as emergence of new promising technologies. Therefore as a practical approach, the Oncofertility Consortium recommends installation of specific oncofertility programs for common cancers such as childhood, breast, and blood cancers according to the contemporary challenges and opportunities. This practical approach will provide efficient oncofertility edification and modeling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients. To carry out this practical approach, the Oncofertility Consortium has designed its new Repro-Can-OPEN Studies (**Repro**duction and **Can**cer in the **O**ncofertility **P**rofessional **E**ngagement **N**etwork).

Recently in our Repro-Can-OPEN Study Part 1 published at *Journal of Assisted Reproduction and Genetics* (JARG) [10], we proposed installation of specific oncofertility programs for common cancers in limited resource settings amidst a current global crisis of the COVID-19 pandemic as well as in 14 developing countries from Africa, Asia, and Latin America. As a further step to reflect the actual wide spectrum of oncofertility practice around the globe and to help provide plausible oncofertility best practice models, we propose here in our Repro-Can-OPEN Study Part 2 installation of specific oncofertility programs for common cancers in optimum resource settings. Our Repro-Can-OPEN Study Part 2 is based on the practical experience of 25 leading and well-resourced oncofertility centers and institutions from the USA, Europe, Australia, and Japan.

Methods

The Oncofertility Consortium sent the Repro-Can-OPEN Study Part 2 questionnaire via email to 25 leading and well-resourced oncofertility centers and institutions from the USA, Europe, Australia, and Japan (Table 1 and Fig. 1) to be proposed for childhood cancer, breast cancer, and blood cancer. The Repro-Can-OPEN Study Part 2 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. The responses for childhood cancer, breast cancer, and blood cancer from the surveyed centers were collected, reviewed, and analyzed.

To analyze the collected data, our coauthor Dr. Salama from Northwestern University developed the new scoring system "oncofertility score". As previously described [10], the oncofertility score is a new diagnostic tool to measure the availability and utilization of oncofertility options for cancer patients in a treating center, country, or group of centers or countries. It is also a prognostic tool to follow up on the development of oncofertility options and strategies provided to cancer patients over time. The oncofertility score is calculated as a percentile ratio between the actual and maximal points of utilization that an oncofertility option might have (Table 2 and 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 rarely used or 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. When the fertility preservation option is not available to cancer patients because it is still in the preclinical research stage, it is marked with (No*). The maximal point 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 of 25 surveyed centers, 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 25 surveyed centers. The total maximal points for an oncofertility option equal 100 points multiplied by 25 (number of surveyed centers in this study) resulting in 2500 points.

Results

All 25 surveyed centers responded to all questions. Each surveyed center has the same serial number in all tables (Tables 1,

Table 1 Surveyed oncofertility centers

N	Surveyed oncofertility centers
1	Oncofertility Consortium, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611, USA. Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Ave, Box 63, Chicago IL, 60611, USA.
2	Yale Fertility Center and Yale Fertility Preservation program, 200 West Campus Dr., Orange, CT 06477, USA.
3	Karolinska Institutet, Department of Oncology-Pathology and Karolinska University Hospital, Department of Reproductive Medicine, Division of Gynecology and Reproduction, SE-14186, Stockholm, Sweden.
4	Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki, Kanagawa, Japan.
5	Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy. Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy.
6	Fertility Preservation Service, Reproductive Services Unit, Royal Women's Hospital, Parkville, 3051, Australia. Fertility Preservation Service, Melbourne IVF, East Melbourne, 3002, Australia.
7	Children's National Hospital, 111 Michigan Avenue NW, Washington, DC 20010, USA (ZIA# HD008985).
8	Center for Reproductive Medicine, Michigan Medicine, 475 Market Place, Building 1, Suite B, Ann Arbor, MI 48108, USA.
9	Fertility Research Centre, Royal Hospital for Women, Barker Street, Sydney, Australia.
10	Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA, USA.
11	University of Edinburgh, Edinburgh, UK. Royal Infirmary of Edinburgh and Royal Hospital for Children and Young People, Little France Crescent, Edinburgh, UK.
12	Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43205, USA.
13	University of Pennsylvania, Division of Reproductive Endocrinology & Infertility, 3701 Market Street, Suite 8000, Philadelphia, PA 19104, USA.
14	New York University, NYU Langone Fertility Center, 660 First Ave, 5th Floor, New York, NY 10016, USA.
15	UniKiD - Center for Reproductive Medicine, UniCareD - Center for Fertility Preservation, Düsseldorf University Hospital, Moorenstrasse 5, D-40225 Düsseldorf, Germany.
16	Laboratory of Reproductive Biology, Juliane Marie Centre for Women, Children and Reproduction, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
17	Fertility Preservation Service, The Royal Children's Hospital, Flemington Rd, Parkville, Melbourne, Vic 3054, Australia.
18	University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92039-0901, USA.
19	Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Avenue Hippocrate, 10, 1200 Brussels, Belgium. Université Catholique de Louvain, Avenue Mounier 52, 1200 Brussels, Belgium.
20	Fertility Clinic and Research Laboratory on Human Reproduction, CUB-Erasme Hospital, Université Libre de Bruxelles (ULB), 808 route de Lennik, 1070 Brussels, Belgium.
21	Centre for Reproductive Medicine of UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
22	Gynecological Endocrinology and Reproductive Medicine Division, Obstetrics and Gynecology Department, Cologne University Hospital, Cologne, Germany.
23	Center for Reproduction and Transplantation, Magee-Womens Hospital, University of Pittsburgh Medical Center, 300 Halket Street, Pittsburgh, PA 15213, USA.
24	University of Cincinnati, Department of Obstetrics and Gynecology, Division for REI, Cincinnati, OH 45229, USA. Cincinnati Children's Hospital Medical Center, Division of Pediatric Adolescent Gynecology Pediatric, Cincinnati, OH 45229, USA.
25	Urology Department, UCSF Medical Center, University of California, San Francisco, CA 94143, USA. Obstetrics and Gynecology Department, UCSF Medical Center, University of California, San Francisco, CA 94143, USA.

3, 4, and 5). Responses for childhood, breast, and blood cancers and their calculated oncofertility scores are listed in Tables 3, 4, and 5.

The oncofertility scores for options provided to children with cancer in all 25 surveyed centers were as follows: gonadal shielding in case of irradiation (69%), ovarian tissue freezing (63%), fractionation of chemo- and radiotherapy (61%), oophoropexy in case of pelvic irradiation (42%), testicular tissue freezing (41%), GnRH analogs in case of old child (9-14 years) (35%), oocyte in vitro maturation (IVM) (18%), neoadjuvant cytoprotective pharmacotherapy (6%), artificial ovary (2%), in vitro spermatogenesis (2%), and stem cells (0%) (Table 3 and Fig. 3).

The oncofertility scores for options provided to female patients with breast cancer in all 25 surveyed centers were as follows: egg freezing (77%), IVF/ICSI of frozen oocytes (75%), gonadal shielding in case of irradiation (75%), embryo freezing (66%), frozen embryo transfer (64%), fractionation of chemo- and radiotherapy (62%), GnRH analogs (61%), ovarian tissue freezing (49%), autotransplantation of frozen

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

ovarian tissue (43%), oocyte in vitro maturation (IVM) (23%), neoadjuvant cytoprotective pharmacotherapy (5%), artificial ovary (2%), and stem cells (0%) (Table 4 and Fig. 4).

The oncofertility scores for options provided to patients with blood cancer in all 25 surveyed centers were as follows: sperm freezing (83%), gonadal shielding in case of irradiation (75%), egg freezing (68%), fractionation of chemo- and radiotherapy (62%), embryo freezing (58%), ovarian tissue freezing (57%), GnRH analogs (57%), oophoropexy in case of pelvic irradiation (46%), testicular tissue freezing (38%), oocyte in vitro maturation (IVM) (23%), neoadjuvant cytoprotective pharmacotherapy (7%), artificial ovary (2%), in vitro spermatogenesis (2%), and stem cells (0%) (Table 5 and Fig. 5).

Discussion

In our Repro-Can-OPEN Study Part 2, the responses and their calculated oncofertility scores (Tables 3, 4, and 5 and Figs. 3, 4, and 5) showed three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy; (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM); and (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cell reproductive technology as they are still in preclinical or early clinical research settings.

Proper technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients including gonadal tissue freezing and autotransplantation, in vitro maturation of gametes, artificial gonad technology, neoadjuvant cytoprotective pharmacotherapy, and stem cell reproductive technology. Technically, the aforementioned advanced oncofertility options are sophisticated procedures that require well-resourced oncofertility centers with expert teams of oncologists, reproductive endocrinology and infertility specialists, pediatric and adolescent gynecologists, urologists, pediatric endocrinologists, biologists, embryologists, scientists, and transplantation surgeons. That is why they should be performed only at highly specialized oncofertility centers in optimum resource settings. Early referral of cancer patients to such highly specialized oncofertility centers is strongly recommended. Ethically, most of these advanced oncofertility options are experimental or have limited data on efficacy, and it is essential that they are offered to patients under clear ethical regulations. Special ethical and legal considerations need to be considered in children [11, 12]. Obtaining ethical approval from the Institutional Review Board (IRB) or the equivalent ethics committee is essential, as is obtaining informed consent from the patients or the legal guardians in the case of a minor. Informed consent for experimental medical treatments and interventions should include the explanation of the procedures, benefits, risks, alternative treatments, and information about the expected outcome and costs. Several oncofertility

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 rarely used or 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%

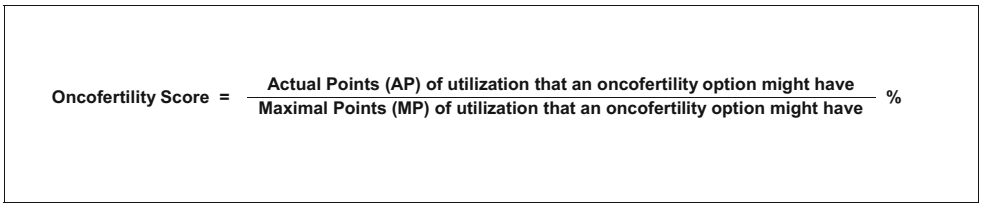

Fig. 2 Oncofertility score calculation

options are expensive and not fully covered by health insurance in some states and countries, leaving many patients under critical financial pressure. In such complex situations, doctors and patient navigators as well as patient support and advocacy organizations can play an important role in reassuring and guiding patients or legal guardians of minors during counseling [13–18].

Installing oncofertility programs in optimum resource settings

Based on the responses and their calculated oncofertility scores (Tables 3, 4, and 5 and Figs. 3, 4, and 5), we will try here to tailor and install plausible oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models (Table 6). Previous international oncofertility guidelines and recommendations were considered as well [19–35]. Immediately after cancer diagnosis, we recommend early referrals of patients to oncofertility specialists to check the anticancer therapy plan and estimate the related risk of gonadotoxicity and subsequent fertility loss. The risk of anticancer therapy-induced gonadotoxicity and fertility loss depends mainly on the type and stage of the disease, type and dose of anticancer therapy, and the age of the patient at the time of treatment. If the risk of gonadotoxicity and fertility loss is detected or even unknown, a comprehensive multidisciplinary oncofertility strategy should be offered before, during, and after anticancer therapy.

From a practical point of view, an effective oncofertility strategy should be individualized and tailored to the patient's circumstances and it may integrate various established, debatable, and experimental options after proper counseling and obtaining informed consent from the patient or the legal guardians of a minor. It is recommended that the proposed oncofertility strategy should include at least one cryopreservation option. After complete cure from cancer, and when the patient decides to have biological children, a new assessment of reproductive functions should be performed. If anticancer therapy-induced gonadal dysfunction exists, fertility restoration may be achieved by using the cryopreserved gametes or gonadal tissue.

Installing oncofertility programs for childhood cancer in optimum resource settings

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, lymphoma, and sarcomas. Unique medical challenges in oncofertility programs for childhood cancer exist and include the following: (1) freezing of gonadal tissues is the only suitable cryopreservation option before puberty, and (2) autotransplantation of frozen gonadal tissue may carry the risk of reintroducing malignant cells, especially in leukemia which is the most common childhood cancer [36–42].

According to the aforementioned unique medical challenges, as well as the responses and their calculated oncofertility scores (Table 3 and Fig. 3), we suggest installing the following oncofertility programs for childhood cancer in optimum resource settings. Before initiation of anticancer therapy, freezing of prepubertal gonadal tissues (ovarian or testicular tissue) should be encouraged and attempted when possible. In vitro maturation and further vitrification of gametes (oocytes or spermatozoa) and artificial gonad technology (ovary or testis) are still experimental and cannot be relied upon as effective oncofertility options in children. Although experimental, these emerging technologies of in vitro maturation of gametes and artificial gonads aim to provide safe alternatives to avoid future gonadal tissue autotransplantation and potential reintroduction of malignant cells. Oophoropexy before female pelvis irradiation should be attempted when possible. During anticancer therapy, gonadal shielding in case of irradiation should be attempted. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Use of GnRH analogs to preserve fertility during chemotherapy in case of older children (9-14 years) is widely debated and needs more research to inform evidence-based practice. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven as an effective oncofertility option. After anticancer therapy, gonadal function should be monitored to ensure appropriate growth, pubertal development, and reproductive function, with hormone replacement introduced in those with gonadal failure. Furthermore, regular follow-up in survivorship offers a window of opportunity for interval fertility and sexual healthcare, linking patients in with the tissue storage laboratory, and discussing

Table 3 Oncofertility options and scores (%) for childhood cancer in all 25 surveyed centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)
Available fertility preservation options for girls with cancer																											
- Ovarian tissue freezing	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++++)	Yes (++)	No	Yes (++)	Yes (++++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (++)	Yes (++)	1575	63
- Oophoropexy in case of pelvic irradiation	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	No	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	1050	42
- Oocyte in vitro maturation (IVM)	No	No	Yes (+)	Yes (++)	No	Yes (+)	No	No	Yes (+)	Yes (+)	No	No	No	No	No	Yes (++)	Yes (++)	No	Yes (+)	Yes (+)	Yes (++)	Yes (++)	No	No	Yes (+)	450	18
- Artificial ovary	No*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	No	Yes (+)	Yes (+)	No	No	50	2
Available fertility preservation options for boys with cancer																											
- Testicular tissue freezing	Yes (++)	Yes (+)	Yes (+)	No	No	Yes (++)	Yes (++)	No	No	Yes (+)	Yes (++)	Yes (+)	Yes (++)	No	Yes (+)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	1025	41
- In vitro spermatogenesis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	Yes (+)	No	Yes (+)	No	No	50	2
Available fertility preservation options for both girls and boys with cancer																											
- GnRH analogs in case of old child (9-14 year)	Yes (++)	Yes (++)	No	No	Yes (+)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	No	No	No	Yes (+)	No	Yes (++)	875	35
- Gonadal shielding in case of irradiation	Yes (+)	Yes (++)	Yes(++)	Yes (+)	Yes (++)	Yes (++)	No	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1725	69
- Fractionation of chemo- and radiotherapy	Yes (++)	Yes (++)	Yes (+++)	No	No	Yes (++)	No	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1525	61
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	Yes (+)	No	No	Yes (+)	Yes (++)	No	No	No	No	No	Yes (+)	No	No	150	6
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	No	0	0

(++++) Available and always used for cancer patients, (+++) available and commonly used for cancer patients, (++) available but occasionally used for cancer patients, (+) available but rarely used or only used in research setting for cancer patients, (No) not available, (No*) not available because it is still in the preclinical research stage

Table 4 Oncofertility options and scores (%) for breast cancer in all 25 surveyed centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)
Available fertility preservation options before anticancer treatment																											
- Embryo freezing	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (+)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	1650	66
- Egg freezing	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (+)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++++)	Yes (+++)	Yes (+++)	Yes (++++)	Yes (+++)	Yes (+++)	1925	77
- Ovarian tissue freezing	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++)	Yes (+++)	Yes (+++)	No	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+)	Yes (++)	1225	49
- Oocyte in vitro maturation (IVM)	Yes (++)	Yes (+)	Yes (+)	Yes (+)	No	Yes (++)	No	No	Yes (++)	Yes (+)	No	No	Yes (+)	Yes (+)	No	Yes (+)	Yes (++)	No	No	Yes (+)	Yes (+++)	Yes (+)	No	No	Yes (+++)	575	23
- Artificial ovary	No*	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No*	No	No	Yes (+)	Yes (+)	No	No	50	2
Available fertility preservation options during anticancer treatment																											
- GnRH analogs	Yes (++)	Yes (+++)	Yes (+)	No	Yes (+++)	Yes (++++)	Yes (+)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	1525	61
- Gonadal shielding in case of irradiation	Yes (++)	Yes (+++)	Yes (++)	No	Yes (+++)	Yes (++++)	Yes (++)	Yes (++++)	Yes (+++)	Yes (++++)	Yes (++++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (++++)	1875	75
- Fractionation of chemo- and radiotherapy	No	Yes (+++)	Yes (++)	No	No	Yes (++++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+)	Yes (++++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	1550	62
- Neoadjuvant cytoprotective pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	No	No	No	Yes (++)	No	No	No	No	No	No	Yes (++)	No	No	125	5
Available fertility restoration options after anticancer treatment																											
- Frozen embryo transfer	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (+)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+++)	1600	64
- IVF/ICSI of frozen oocytes	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (+)	Yes (++)	Yes (+++)	Yes (++)	Yes (+++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++++)	Yes (+++)	Yes (+++)	Yes (++++)	Yes (+++)	Yes (+++)	1875	75
- Autotransplantation of frozen ovarian tissue	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	No	Yes (++)	Yes (+)	Yes (++)	No	Yes (+)	No	Yes (++)	Yes (+++)	Yes (+++)	No	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (+)	Yes (+)	1075	43
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0	0

(++++) Available and always used for cancer patients, (+++) available and commonly used for cancer patients, (++) available but occasionally used for cancer patients, (+) available but rarely used or only used in research setting for cancer patients, (No) not available, (No*) not available because it is still in the preclinical research stage

Table 5 Oncofertility options and scores (%) for blood cancer in all 25 surveyed centers

Oncofertility Center	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total Actual Points	Oncofertility Score (%)
Available fertility preservation options for female patients																											
- Embryo freezing	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1450	58
- Egg freezing	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (+++)	Yes (+)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	1700	68
- Ovarian tissue freezing	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	No	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (+)	No	Yes (+++)	Yes (++)	Yes (+++)	No	No	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++)	1425	57
- Oophoropexy in case of pelvic irradiation	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (+)	Yes (+++)	Yes (+)	Yes (+)	Yes (+)	Yes (++)	Yes (++)	Yes (+)	Yes (+)	Yes (+)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	1150	46
- Oocyte in vitro maturation (IVM)	Yes (++)	Yes (+)	Yes (+)	Yes (++)	No	Yes (++)	No	No	Yes (+)	Yes (+)	No	No	Yes (+)	Yes (+)	No	Yes (+)	Yes (++)	No	No	Yes (+)	Yes (+++)	Yes (+)	No	No	Yes (+++)	575	23
- Artificial ovary	No'	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No'	No	No	Yes (+)	Yes (+)	No	No	50	2
Available fertility preservation options for male patients																											
- Sperm freezing	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++++)	Yes (++++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (+++)	2075	83
- Testicular tissue freezing	Yes (++)	Yes (+)	Yes (+)	No	No	Yes (++++)	Yes (+)	No	No	Yes (+)	Yes (++)	Yes (+)	Yes (+)	No	Yes (++)	Yes (+)	Yes (++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (+)	Yes (+++)	Yes (+++)	Yes (+++)	Yes (+++)	950	38
- In vitro spermatogenesis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No'	No	Yes (+)	No	Yes (+)	No	No	50	2
Available fertility preservation options for both female and male patients																											
- GnRH analogs	Yes (++)	Yes (++)	Yes (+)	No	Yes (++)	Yes (++++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (+)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	No	Yes (+++)	1425	57
- Gonadal shielding in case of irradiation	Yes (++)	Yes (++)	Yes (++)	No	Yes (++++)	Yes (++)	Yes (+++)	Yes (+++)	Yes (++++)	Yes (+++)	Yes (++++)	Yes (++++)	Yes (++++)	Yes (++)	Yes (++)	Yes (++)	Yes (+++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++++)	Yes (+++)	1875	75
- Fractionation of chemo- and radiotherapy	Yes (++)	Yes (++)	Yes (++)	No	No	Yes (+++)	Yes (++)	Yes (+++)	Yes (++++)	Yes (+)	Yes (+++)	Yes (++)	Yes (++++)	Yes (++)	Yes (+++)	Yes (+)	Yes (++)	Yes (++)	Yes (+++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	Yes (++)	1550	62
- Neoadjuvant cytoreductive pharmacotherapy	No	No	No	No	No	No	No	No	Yes (+)	No	No	No	No	No	No	Yes (+)	Yes (++)	No	No	No	No	No	Yes (+)	No	No	175	7
- Stem cells reproductive technology	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No'	No	No	0	0

(++++) Available and always used for cancer patients, (+++) available and commonly used for cancer patients, (++) available but occasionally used for cancer patients, (+) available but rarely used or only used in research setting for cancer patients, (No) not available, (No*) not available because it is still in the preclinical research stage

expectations around relationships, pregnancy, and parenthood [43]. When the patient becomes an adult and wishes to have children, fertility restoration may be possible using stored gonadal tissue or gametes. Autotransplantation of gonadal tissue can be offered to restore fertility but it should be handled with caution in patients with leukemia due to possible contamination of gonadal tissue with leukemic cells. According to few reports, harvesting gonadal tissue after the first cycles of anticancer therapy and during complete remission followed by proper gonadal tissue assessment for minimal residual disease (MRD) may reduce the risk of reintroducing leukemic cells with autotransplantation [44, 45]. For additional safety measures, it may be a possible option for patients with leukemia to remove the transplanted gonadal tissue later after restoring fertility and having biological children [46, 47]. Stem cell reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

Installing oncofertility programs for breast cancer in optimum resource settings

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 significantly higher risks to develop breast and ovarian cancers (hereditary breast-ovarian cancer syndrome; HBOC), and they should receive appropriate oncofertility care as well. According to a recent large study, the cumulative breast cancer risk is 72% for *BRCA1* and 69% for *BRCA2* carriers, while the cumulative ovarian cancer risk is 44% for *BRCA1* and 17% for *BRCA2* carriers [48]. Unique medical challenges in oncofertility programs for breast cancer exist and include the following: (1) conventional ovarian stimulation prior to egg or embryo freezing results in elevated serum estradiol levels that should be avoided in estrogen sensitive malignancies such as breast cancer, and (2) autotransplantation of frozen ovarian tissue in patients with *BRCA* mutations should be handled with caution due to significantly higher risks of developing ovarian cancer [49–53].

According to the aforementioned unique medical challenges as well as the responses and their calculated oncofertility scores (Table 4 and Fig. 4), we suggest installing the following oncofertility programs for breast cancer in optimum resource settings. Before initiation of anticancer therapy, freezing of eggs or embryos should be attempted with a random-start protocol for controlled ovarian stimulation and using letrozole or tamoxifen to avoid high estradiol levels. Freezing of ovarian tissue should be attempted when possible. In vitro maturation and further vitrification of oocytes retrieved in vivo or ex vivo from the extracted ovarian tissue (ovarian tissue oocytes in vitro maturation; OTO-IVM) could be attempted [54–56]. Artificial ovary technology is still experimental and cannot be relied upon alone as an

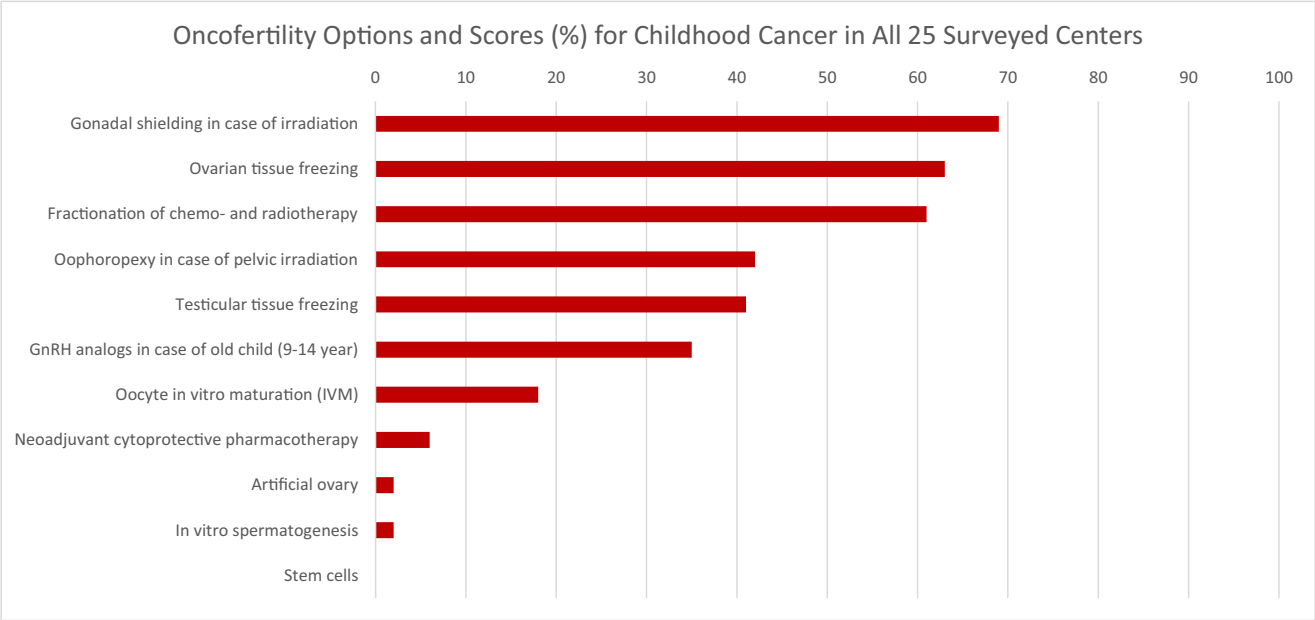

Fig. 3 Oncofertility options and scores (%) for childhood cancer in all 25 surveyed centers

effective oncofertility option. Although experimental, oocyte IVM and artificial ovary technology aim to provide safe alternatives to avoid future ovarian tissue autotransplantation and potential reintroduction of malignant cells. During anticancer therapy, GnRH analog administration before and during chemotherapy can be considered. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Gonadal shielding might be needed in case of combined irradiation to ovaries. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven as an effective oncofertility option. After anticancer therapy, fertility restoration may be achieved by frozen embryo transfer, or in vitro fertilization of stored oocytes. Patients with *BRCA* mutations could be advised to use preimplantation genetic testing (PGT) during in vitro fertilization to avoid transmitting the mutation. Autotransplantation of frozen ovarian tissue can be offered to restore fertility but it should be handled with caution in patients with *BRCA* mutations due to significantly higher risks of developing ovarian cancer. Proper ovarian tissue assessment in patients with *BRCA* mutations is mandatory to reduce the risk of reintroducing malignant cells with autotransplantation. For additional safety measures, it may be a possible option for patients with *BRCA* mutations to remove the transplanted ovarian tissue as well as the remaining ovary (if any) after childbearing is complete and at the time of an elective caesarian section. Stem cell reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

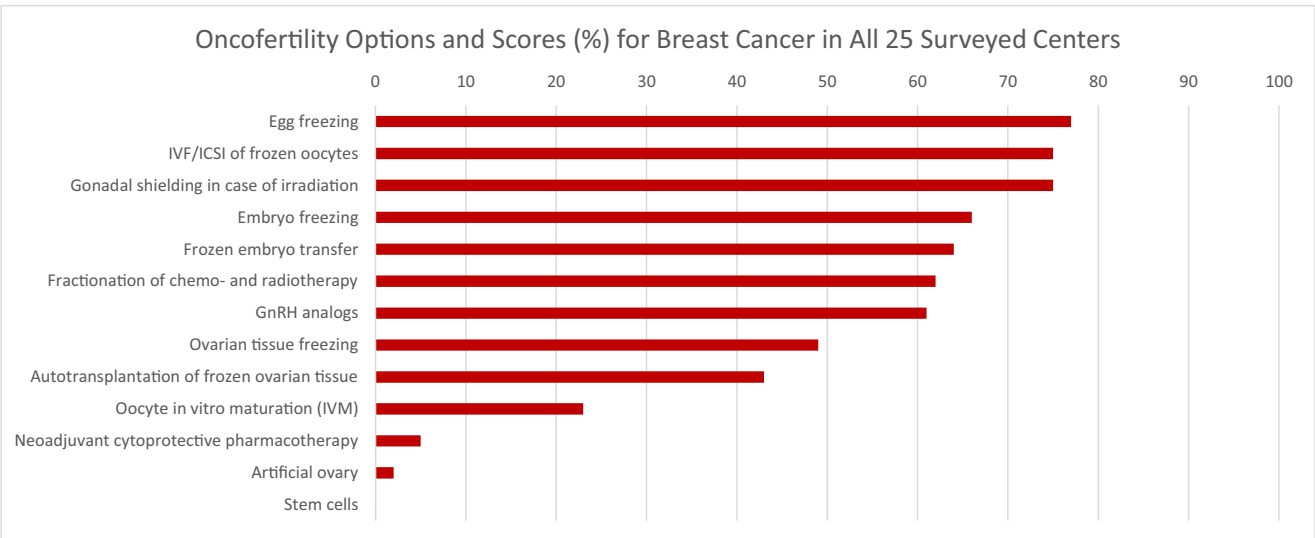

Fig. 4 Oncofertility options and scores (%) for breast cancer in all 25 surveyed centers

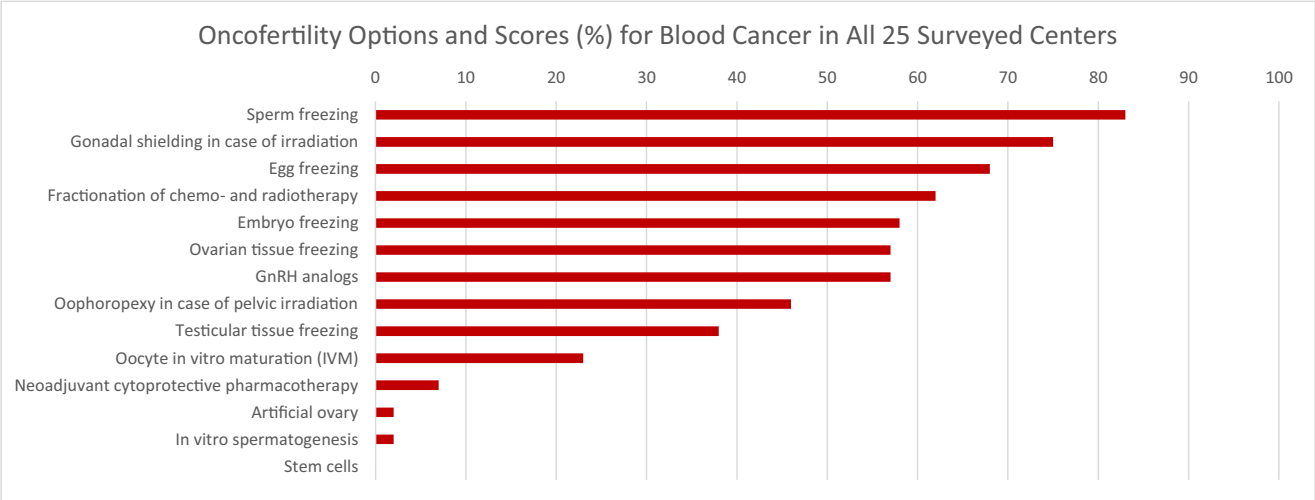

Fig. 5 Oncofertility options and scores (%) for blood cancer in all 25 surveyed centers

Installing oncofertility programs for blood cancer in optimum resource settings

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). Unique medical challenges in oncofertility programs for blood cancer exist and include the following: (1) most cases of blood cancer especially leukemia necessitate immediate initiation of anticancer therapy leaving very short time to offer fertility preservation options, thus may be precluded by the health status of the patient and the time available, and (2) autotransplantation of frozen gonadal tissue may carry the risk of reintroducing malignant cells, especially in leukemia [57–59].

According to the aforementioned unique medical challenges as well as the responses and their calculated oncofertility scores (Table 5 and Fig. 5), we suggest installing the following oncofertility programs for blood cancer in optimum resource settings. Before initiation of anticancer therapy, freezing of embryos or gametes (oocytes or spermatozoa) should be attempted when possible. Freezing of gonadal tissues (ovarian or testicular tissue) should be attempted after proper tissue assessment to exclude contamination with malignant cells. In vitro maturation and further vitrification of gametes retrieved in vivo or ex vivo from the extracted gonadal tissue could be attempted. Artificial gonad technology is still experimental and cannot be relied upon alone as an effective oncofertility option. Although experimental, these emerging technologies of in vitro maturation of gametes and artificial gonads aim to provide safe alternatives to avoid future gonadal tissue autotransplantation and potential reintroduction of malignant cells. Oophoropexy before female pelvis irradiation should be attempted when possible. During anticancer therapy, gonadal shielding in case of irradiation should be attempted. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Use of GnRH analogs to preserve fertility during chemotherapy in case of hematological malignancies is widely debated and needs more research to inform evidence-based practice. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven 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 frozen gonadal tissue can be offered to restore fertility but it should be handled with caution in patients with leukemia due to possible contamination of gonadal tissue with leukemic cells. According to a few reports, harvesting gonadal tissue after the first cycles of anticancer therapy and during complete remission followed by proper gonadal tissue assessment for minimal residual disease (MRD) may reduce the risk of reintroducing leukemic cells with autotransplantation. For additional safety measures, it may be a possible option for patients with leukemia to remove the transplanted gonadal tissue later after restoring fertility and having biological children [46, 47]. Stem cell reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 6).

After installation of these specific oncofertility programs for common cancers in optimum resource settings, we encourage using the “oncofertility score” as a prognostic tool to follow up on the development of these new oncofertility programs over time.

In cases where oncofertility options are rejected, contraindicated, infeasible, unsuccessful, or unavailable, adoption and

Table 6 Suggested best practice models: plausible fertility preservation and restoration strategies for cancer patients

Cancer Patients	Before anticancer therapy (Fertility Preservation)	During anticancer therapy (Fertility Preservation)	After anticancer therapy (Fertility Restoration)
Childhood Cancer (♀ & ♂) Leukemias, central nervous system cancers, lymphoma and sarcomas	- Freezing of gonadal tissue - In vitro maturation and vitrification of gametes (promising in research but not yet clinically proven in children) - Oophoropexy in case of female pelvic radiation - Artificial gonads technology (promising in research but not yet clinically proven)	- Gonadal shielding - Fractionation of chemo- and radiotherapy - GnRH analogs in case of old child (widely debated) - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven)	- IVF/ICSI of frozen gametes - Autotransplantation of frozen gonadal tissue (should be utilized with caution in leukemia) - Stem cells (promising in research but not yet clinically proven)
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 (promising in research but not yet clinically proven)	- GnRH analogs - Fractionation of chemo- and radiotherapy - Gonadal shielding - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven)	- Intrauterine transfer of frozen embryo - IVF/ICSI of frozen oocytes - Autotransplantation of frozen ovarian tissue (should be utilized with caution in BRCA mutations) - Stem cells (promising in research but not yet clinically proven)
Blood Cancer (♀ & ♂) Leukemia (ALL, AML), and Lymphoma (NHL, HL)	- Freezing of gametes (when possible) - Freezing of gonadal tissue - In vitro maturation and vitrification of gametes - Oophoropexy in case of female pelvic radiation - Artificial gonads technology (promising in research but not yet clinically proven)	- GnRH analogs (widely debated) - Gonadal shielding - Fractionation of chemo- and radiotherapy - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven)	- Intrauterine transfer of frozen embryo - IVF/ICSI of frozen gametes - Autotransplantation of frozen gonadal tissue (should be utilized with caution in leukemia) - Stem cells (promising in research but not yet clinically proven)

third-party reproduction, such as sperm, egg, and embryo donation and surrogacy, can be offered as family building alternatives.

Next steps and future directions of Repro-Can-OPEN Studies

In our next Repro-Can-OPEN studies, we are planning to investigate in detail the oncofertility programs offered to leukemia and lymphoma patients according to their gender and age group. We are planning also to investigate other cancers as well as other patient groups (e.g., LGBTQ population: lesbian, gay, bisexual, transgender, and queer or questioning) who were not included in our previous studies. We will provide further discussions on the advanced and the emerging oncofertility options, and highlight the recent achievements in the related preclinical research [60–65]. The Oncofertility Consortium will continue to engage more stakeholders from the USA and abroad to help build a sustainable oncofertility core competency worldwide.

Conclusion

Our Repro-Can-OPEN Study Part 2 proposed installing specific oncofertility programs for common cancers in optimum resource settings as an extrapolation for best practice models. Responses for childhood, breast, and blood cancers and their calculated oncofertility scores showed three major characteristics of oncofertility practice in optimum resource settings: (1) strong utilization of sperm freezing, egg freezing, embryo freezing, ovarian tissue freezing, gonadal shielding, and fractionation of chemo- and radiotherapy; (2) promising utilization of GnRH analogs, oophoropexy, testicular tissue freezing, and oocyte in vitro maturation (IVM); and (3) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, in vitro spermatogenesis, and stem cell reproductive technology as they are still in preclinical or early clinical research settings. Proper technical and ethical concerns should be considered when offering advanced and experimental oncofertility options to patients. Dissemination of our study results and recommendations will provide efficient oncofertility edification and modeling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their patients.

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Compliance with ethical standards

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FERTILITY PRESERVATION

Installing oncofertility programs for breast cancer in limited versus optimum resource settings: Empirical data from 39 surveyed centers in Repro-Can-OPEN Study Part I & II

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Abstract

Purpose As a further step to elucidate the actual diverse spectrum of oncofertility practices for breast cancer around the globe, we present and discuss the comparisons of oncofertility practices for breast cancer in limited versus optimum resource settings based on data collected in the Repro-Can-OPEN Study Part I & II.

Methods We surveyed 39 oncofertility centers including 14 in limited resource settings from Africa, Asia & Latin America (Repro-Can-OPEN Study Part I), and 25 in optimum resource settings from the United States, Europe, Australia and Japan (Repro-Can-OPEN Study Part II). Survey questions covered the availability of fertility preservation and restoration options offered to young female patients with breast cancer as well as the degree of utilization.

Results In the Repro-Can-OPEN Study Part I & II, responses for breast cancer and calculated oncofertility scores showed the following characteristics: (1) higher oncofertility scores in optimum resource settings than in limited resource settings especially for established options, (2) frequent utilization of egg freezing, embryo freezing, ovarian tissue freezing, GnRH analogs, and fractionation of chemo- and radiotherapy, (3) promising utilization of oocyte in vitro maturation (IVM), (4) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, and stem cells reproductive technology as they are still in preclinical or early clinical research settings, (5) recognition that technical and ethical concerns should be considered when offering advanced and innovative oncofertility options.

Conclusions We presented a plausible oncofertility best practice model to guide oncofertility teams in optimizing care for breast cancer patients in various resource settings.

Keywords Oncofertility · Breast cancer · Fertility preservation · Best practice · Limited resource settings · Optimum resource settings

Introduction

Breast cancer is the most common cancer impacting women of reproductive age [1]. Contemporary breast cancer treatment often requires aggressive gonadotoxic therapies that necessitates fertility preservation treatments for those who desire future fertility. Young women with breast cancer have a higher risk of carrying pathologic mutations in the *BRCA1* or *BRCA2* genes, adding further complexity to their oncofertility counseling [2]. According to the most recent international guidelines from the American Society of Clinical Oncology (ASCO) [3], the American Society for Reproductive Medicine (ASRM) [4], the European Society of Human Reproduction and Embryology (ESHRE) [5] and the European Society for Medical Oncology (ESMO) [6], several established, debatable, and experimental oncofertility options can be offered to young female patients with breast cancer to preserve and restore fertility. Established oncofertility options include embryo cryopreservation, oocyte cryopreservation, and recently ovarian tissue cryopreservation and autotransplantation. Debatable options

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for fertility preservation for breast cancer patients include GnRH analogs and hormonal suppression, fractionation of chemotherapy and radiotherapy. Experimental oncofertility options include oocyte in vitro maturation (IVM), artificial ovary, neoadjuvant cytoprotective pharmacotherapy, stem cell reproductive technology and others [3–6].

Despite recognition as official recommendations, oncofertility international guidelines face several challenges in practice. Over the past years, the Oncofertility Consortium has studied oncofertility practices in many countries within its Oncofertility Professional Engagement Network (OPEN) [7, 8]. Our previous studies identified a variety of standards and challenges in oncofertility practices worldwide [9–13]. Recently in our Repro-Can-OPEN Study Part I & II, we proposed installation of specific oncofertility programs for childhood, breast, and blood cancers in limited versus optimum resource settings. The main objectives of Repro-Can-OPEN Study Part I & II were to measure empirically the availability and degree of utilization of oncofertility options provided by the surveyed centers, to identify different styles of oncofertility practice for common cancers in limited and optimum resource settings, and to suggest best practice models for oncofertility care based on the results of the survey and the existing literature [14, 15].

Limited resource settings include the following criteria especially in low- and middle-income countries (Fig. 1): shortage of reproductive care services provided to young patients with cancer, lack of experienced oncofertility teams and necessary equipment, lack of national registries for in vitro fertilization (IVF) and/or cancer treatments, lack of awareness among providers and patients, cultural and religious constraints, partial or complete legal prohibition of third-party reproduction, lack of insurance coverage for IVF and/or cancer treatments resulting in high out-of-pocket costs for patients, and lack of funding to support oncofertility programs. Even in developed countries, a state of limited resource settings could be experienced where access is limited or in case of sudden national disasters when most of public services including healthcare are negatively affected as occurred recently during COVID-19 pandemic and its related economic shutdown. Additionally, within developed countries there may be specific regions that may qualify as limited resource [14].

Optimum resource settings include the following criteria especially in high-income countries (Fig. 1): availability of reproductive care services provided to young patients with cancer, availability of experienced oncofertility teams and necessary equipment, presence of national registries for IVF and cancer treatments, awareness among providers and patients, minimal cultural or religious constraints, legally allowed third-party reproduction, insurance coverage for IVF and cancer treatments, and availability of funding to support oncofertility programs [15].

As a further step to reflect the actual diverse spectrum of oncofertility practices for breast cancer around the globe and to help provide a plausible oncofertility best practice model, this study sought to compare oncofertility practices for breast cancer in limited versus optimum resource settings according to data reported in the Repro-Can-OPEN Study Part I & II.

Methods

The Oncofertility Consortium sent the Repro-Can-OPEN Study questionnaire via email to 39 oncofertility centers in total; 14 oncofertility centers with limited resource settings from Africa, Asia & Latin America in Repro-Can-OPEN Study Part I, and 25 oncofertility centers with optimum resource settings from the United States, Europe, Australia and Japan in Repro-Can-OPEN Study Part II (Table 1). The Repro-Can-OPEN Study questionnaire included questions on the availability of fertility preservation options provided to young female patients with breast cancer in their reproductive years (age < 40 yr.), and whether these options are always, commonly, occasionally or rarely used. Responses

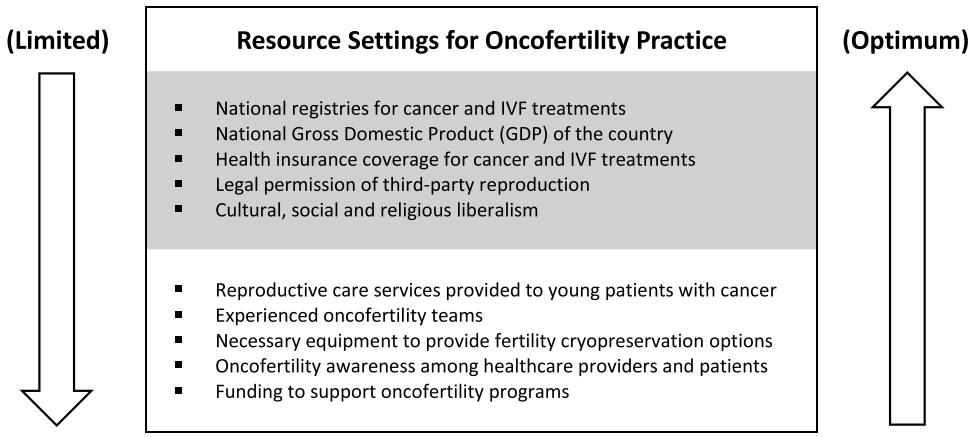

Fig. 1 Limited versus optimum resource settings affecting oncofertility practice on national (grey) and local (white) levels

Table 1 The 39 Surveyed Oncofertility Centers in Repro-Can-OPEN Study Part I & II

Surveyed Oncofertility Centers with Limited Resource Settings (Repro-Can-OPEN Study Part I): ($n=14$)	
1	National Research Center, Cairo, Egypt
2	Aziza Othmana Hospital of Tunis, Tunisia FERTILLA, Clinique la Rose, Tunis, Tunisia
3	Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
4	Laboratorio de Biología Reproductiva y Preservación de la Fertilidad, Laboratorios de Investigación y Desarrollo, Universidad Peruana Cayetano Heredia, Lima, Peru Unidad de Oncología Pediátrica, Hospital Edgardo Rebagliati Martins, Lima, Peru
5	Panama Fertility, Sistema Nacional de Investigadores, Panama City, Panama
6	Pregna Medicina Reproductiva, Buenos Aires, Argentina Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina Procrearte, Buenos Aires, Argentina Hospital de Niños Victor J. Vilela. Rosario, Santa Fe, Argentina
7	Centro de Reproduccion Humana, Facultad de Medicina, Universidad de Valparaiso, Valparaiso, Chile
8	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
9	Fertility Preservation Centre, Department of Clinical Embryology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India Department of Medical Oncology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India Mother and Child Hospital, New Delhi, India Dr. Patil's Fertility and Endoscopy Clinic, Bangalore, India Hospital Institute of Medical Sciences & SRCC children's Hospital, Mumbai, India
10	Vitalab Fertility Centre, Johannesburg, South Africa Department Medical Oncology, University of Witwatersrand, Johannesburg, South Africa Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa
11	Instituto Nacional de Cancerología, Bogota, Colombia FERTIVIDA Fertility Center, Bogota, Colombia
12	Instituto Guatemalteco de Seguridad Social (IGSS), Guatemala City, Guatemala
13	Thuriah Medical Center, Riyadh, Kingdom of Saudi Arabia
14	The Oncology and Fertility Centres of Ekocorp Plc, Eko Hospitals, Lagos, Nigeria Kingswill Specialist Hospital, Lagos, Nigeria
Surveyed Oncofertility Centers with Optimum Resource Settings (Repro-Can-OPEN Study Part II): ($n=25$)	
1	Oncofertility Consortium, Feinberg School of Medicine, Northwestern University, Chicago, IL 60,611, USA Ann & Robert H. Lurie Children's Hospital of Chicago, 225 East Chicago Ave, Box 63, Chicago IL, 60,611, USA
2	Yale Fertility Center and Yale Fertility Preservation program, 200 West Campus Dr., Orange, CT 06,477, USA
3	Karolinska Institutet, Department of Oncology-Pathology and Karolinska University Hospital, Department of Reproductive Medicine, Division of Gynecology and Reproduction, SE-14186, Stockholm, Sweden
4	Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, 2–16-1, Sugao, Miyamae-ku, Kawasaki, Kanagawa, Japan
5	Department of Medical Oncology, UOC Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Genova, Italy Department of Internal Medicine and Medical Specialties (DiMI), School of Medicine, University of Genova, Genova, Italy
6	Fertility Preservation Service, Reproductive Services Unit, Royal Women's Hospital, Parkville, 3051, Australia Fertility Preservation Service, Melbourne IVF, East Melbourne, 3002, Australia
7	Children's National Hospital, 111 Michigan Avenue NW, Washington, DC 20,010, USA. (ZIA# HD008985)
8	Center for Reproductive Medicine, Michigan Medicine, 475 Market Place, Building 1, Suite B, Ann Arbor, MI 48,108, USA

Table 1 (continued)

Surveyed Oncofertility Centers with Limited Resource Settings (Repro-Can-OPEN Study Part I): ($n = 14$)	
9	Fertility Research Centre, Royal Hospital for Women, Barker Street, Sydney, Australia
10	Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA, USA
11	University of Edinburgh, Edinburgh, UK Royal Infirmary of Edinburgh and Royal Hospital for Children and Young People, Little France Crescent, Edinburgh, UK
12	Nationwide Children's Hospital, 700 Children's Dr., Columbus, OH 43,205, USA
13	University of Pennsylvania, Division of Reproductive Endocrinology & Infertility, 3701 Market Street, Suite 8000, Philadelphia, PA 19,104, USA
14	New York University, NYU Langone Fertility Center, 660 First Ave, 5th Floor, New York, NY 10,016, USA
15	UniKiD—Center for Reproductive Medicine, UniCareD—Center for Fertility Preservation, Düsseldorf University Hospital, Moorenstrasse 5, D-40225 Düsseldorf, Germany
16	Laboratory of Reproductive Biology, Juliane Marie Centre for Women, Children and Reproduction, University Hospital of Copenhagen, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
17	Fertility Preservation Service, The Royal Children's Hospital, Flemington Rd, Parkville, Melbourne, Vic 3054, Australia
18	University of California, San Diego, 3855 Health Sciences Drive, La Jolla, CA 92,039–0901, USA
19	Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Avenue Hippocrate, 10, 1200 Brussels, Belgium Université Catholique de Louvain, Avenue Mounier 52, 1200 Brussels, Belgium
20	Fertility Clinic and Research Laboratory on Human Reproduction, CUB-Erasme Hospital, Université Libre de Bruxelles (ULB), 808 route de Lennik, 1070 Brussels, Belgium
21	Centre for Reproductive Medicine of UZ Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium
22	Gynecological Endocrinology and Reproductive Medicine Division, Obstetrics and Gynecology Department, Cologne University Hospital, Cologne, Germany
23	Center for Reproduction and Transplantation, Magee-Womens Hospital, University of Pittsburgh Medical Center, 300 Halket Street, Pittsburgh, PA 15,213, USA
24	University of Cincinnati, Department of Obstetrics and Gynecology, Division for REI, Cincinnati, OH 45,229, USA Cincinnati Children's Hospital Medical Center, Division of Pediatric Adolescent Gynecology Pediatric, Cincinnati, OH 45,229, USA
25	Urology Department, UCSF Medical Center, University of California, San Francisco, CA 94,143, USA Obstetrics and Gynecology Department, UCSF Medical Center, University of California, San Francisco, CA 94,143, USA

from oncofertility medical teams from surveyed centers were collected, reviewed, and analyzed.

To analyze the collected data, we developed a new scoring system, 'the oncofertility score' [14, 15]. As previously described, the oncofertility score is a new diagnostic tool to measure the availability and degree of utilization of oncofertility options for cancer patients in a treating center, country, or group of centers or countries. Although empirical, the oncofertility score could be also used as a prognostic tool to follow up on the development of oncofertility options and strategies provided to cancer patients over time especially in absence of accurate national oncofertility registries. The 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 rarely used or 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. When

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 rarely used or 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%

Fig. 2 Oncofertility Score calculation

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

the fertility preservation option is not available to cancer patients because it is still in the preclinical research stage, it is marked with (No*). 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 +) [14, 15].

In our Repro-Can-OPEN Study Part I & II, the oncofertility score was 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 the surveyed centers. The total maximal points for an oncofertility option equal 100 points multiplied by the number of surveyed centers [14, 15].

Results

Based on data collected in the Repro-Can-OPEN Study Part I & II, all 39 surveyed centers responded to all questions. The oncofertility scores (%) for options provided to young female patients with breast cancer in the 14 centers with limited resource settings versus in the 25 centers with optimum resource settings, respectively, were as follows (Table 3 & Fig. 3);

Available fertility preservation options before anticancer treatment

Embryo freezing (55.35 vs66), egg freezing (58.92 vs 77), ovarian tissue freezing (28.57 vs 49), oocyte in vitro maturation (IVM) (28.57 vs 23) and artificial ovary (1.78 vs 2).

Available fertility preservation options during anticancer treatment

GnRH analogs (55.35 vs 61), fractionation of chemo- and radiotherapy (62.5 vs 62) and neoadjuvant cytoprotective pharmacotherapy (1.78 vs 5).

Available fertility restoration options after anticancer treatment

Frozen embryo transfer (53.57 vs 64), IVF/ICSI of frozen oocytes (55.35 vs 75), autotransplantation of frozen ovarian tissue (19.64 vs 43) and stem cells reproductive technology (3.57 vs 0).

Discussion

Oncofertility options and scores for breast cancer in limited versus optimum resource settings

In our Repro-Can-OPEN Study Part I & II, the responses for breast cancer and their calculated oncofertility scores (Table 3 & Fig. 3) showed the following characteristics: (1) Higher oncofertility scores in optimum resource settings than in limited resource settings especially for established options, (2) frequent utilization of egg freezing, embryo freezing, ovarian tissue freezing, GnRH analogs, and fractionation of chemo- and radiotherapy, (3) promising utilization of oocyte in vitro maturation (IVM), (4) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, and stem cells reproductive technology as

Table 3 Oncofertility Options and Scores (%) for Breast Cancer in Limited versus Optimum Resource Settings, based on empirical data from 39 surveyed centers in Repro-Can-OPEN Study Part I & II [14, 15]

Oncofertility Options and Scores (%) for Breast Cancer	Centers with Limited Resource Settings (Repro-Can-OPEN Study I) ($n=14$)	Centers with Optimum Resource Settings (Repro-Can-OPEN Study II) ($n=25$)
Available fertility preservation options before anticancer treatment		
Embryo freezing	55.35	66
Egg freezing	58.92	77
Ovarian tissue freezing	28.57	49
Oocyte in vitro maturation (IVM)	28.57	23
Artificial ovary	1.78	2
Available fertility preservation options during anticancer treatment		
GnRH analogs	55.35	61
Fractionation of chemo- and radiotherapy	62.5	62
Neoadjuvant cytoprotective pharmacotherapy	1.78	5
Available fertility restoration options after anticancer treatment		
Frozen embryo transfer	53.57	64
IVF/ICSI of frozen oocytes	55.35	75
Autotransplantation of frozen ovarian tissue	19.64	43
Stem cells reproductive technology	3.57	0

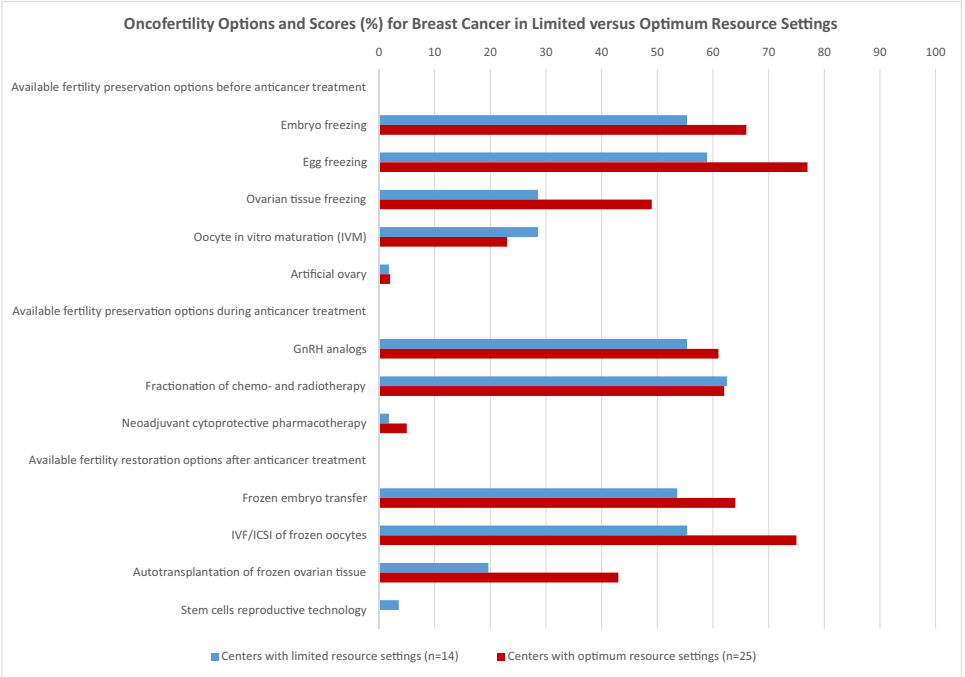

Fig. 3 Oncofertility Options and Scores (%) for Breast Cancer in Limited versus Optimum Resource Settings, based on empirical data from 39 surveyed centers in Repro-Can-OPEN Study Part I & II [14, 15]

they are still in preclinical or early clinical research settings, (5) recognition that proper technical and ethical concerns should be considered when offering advanced and innovative oncofertility options to patients including ovarian tissue freezing and autotransplantation, oocyte in vitro maturation (IVM), artificial ovary technology, neoadjuvant cytoprotective pharmacotherapy and stem cells reproductive technology. Technically, the aforementioned advanced and innovative oncofertility options are sophisticated procedures that require well-resourced oncofertility centers with expert teams of oncologists, reproductive endocrinology and infertility specialists, gynecologists, biologists, embryologists,

scientists, and transplantation surgeons. Early referral of breast cancer patients to highly specialized oncofertility centers is strongly recommended.

Recently in 2019, the American Society for Reproductive Medicine Committee Opinion on fertility preservation in patients undergoing gonadotoxic therapies stated that ovarian tissue freezing and autotransplantation should be considered an established medical procedure and no longer considered experimental [4]. Afterwards in 2020, the ESHRE guideline also considered ovarian tissue freezing and autotransplantation non-experimental but used the term 'innovative' rather than established to reflect the evidence base [5]. However, oocyte in vitro maturation (IVM), artificial ovary technology, neoadjuvant cytoprotective pharmacotherapy and stem cells reproductive technology are still considered experimental and have limited data on efficacy, and it is essential that they are offered to patients strictly under clear ethical regulations. Obtaining ethical approval from the Institutional Review Board (IRB) or the equivalent ethics committee is essential, as is obtaining informed consent from the patients. Informed consent for experimental medical treatments and interventions should include the explanation of the procedures, benefits, risks, alternative treatments, and information about the expected outcome and costs. Several oncofertility options are expensive and not fully covered by health insurance in many states and countries, leaving many patients under acute financial pressure at the time of a life-altering cancer diagnosis. In such complex situations, doctors and patient navigators as well as patient support and advocacy organizations can play an important role in reassuring and guiding patients [16–18].

General considerations for oncofertility care of breast cancer

Based on the responses and their calculated oncofertility scores (Table 3 & Fig. 3), we propose to design and install plausible oncofertility programs for breast cancer as an extrapolation for a best practice model (Table 4). Existing literature and international oncofertility guidelines and recommendations were also considered [3–6, 19–35]. Immediately after a breast cancer diagnosis, we recommend early referrals of patients to the oncofertility team to review the cancer therapy plan and estimate the related risk of gonadotoxicity and subsequent fertility loss. The risk of anticancer therapy-induced gonadotoxicity and fertility loss depends mainly on the type and stage of the disease, type and dose of anticancer therapy as well as the age of the patient and her ovarian reserve at the time of treatment. If the risk of gonadotoxicity and fertility loss is detected or even unknown, a comprehensive multidisciplinary oncofertility strategy should be offered before, during and after anticancer therapy.

Table 4 Suggested best practice model: Plausible fertility preservation and restoration strategies for breast cancer patients

Cancer Patients	Before anticancer therapy (Fertility Preservation)	During anticancer therapy (Fertility Preservation)	After anticancer therapy (Fertility Restoration)
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 (promising in research but not yet clinically proven)	- GnRH analogs - Fractionation of chemo- and radiotherapy - Ovarian shielding in case of combined pelvic irradiation - Neoadjuvant cytoprotective pharmacotherapy (promising in research but not yet clinically proven)	- Intrauterine transfer of frozen embryo - IVF/ICSI of frozen oocytes - Autotransplantation of frozen ovarian tissue (should be utilized with caution in BRCA mutations) - Stem cells (promising in research but not yet clinically proven)

From a practical point of view, an effective oncofertility strategy should be individualized and tailored to the patient's circumstances and it may integrate various established, debatable, and experimental options after proper counselling and obtaining informed consent from the patient. It is recommended that a proposed oncofertility strategy should include at least one cryopreservation option. After complete cure or extended remission from cancer, and when the patient decides to have biological children, a new assessment of reproductive function should be performed. If anticancer therapy-induced premature ovarian insufficiency (POI), fertility restoration may be achieved by using the cryopreserved eggs, embryos or ovarian tissue [36–38].

Installing oncofertility programs for female patients with breast cancer

In addition to breast cancer patients, women with *BRCA* mutations have several concerns that can affect their reproductive potential. A recent study showed that women with *BRCA* mutations not only have a lower basal ovarian reserve but also are more likely to lose it after chemotherapy. These findings highlight the importance of offering fertility preservation options to such patients [39]. Furthermore, women with *BRCA* mutations carry significantly higher risks to develop breast and ovarian cancers (Hereditary Breast-Ovarian Cancer Syndrome; HBOC), and they should receive appropriate oncofertility care as well. According to a recent large study, the cumulative breast cancer risk is 72% for *BRCA1* and 69% for *BRCA2* carriers, while the cumulative ovarian cancer risk is 44% for *BRCA1* and 17% for *BRCA2* carriers [40].

Unique medical challenges in oncofertility programs for breast cancer exist and include (1) conventional ovarian stimulation prior to egg or embryo freezing results in elevated serum estradiol levels that should be avoided in estrogen sensitive malignancies such as breast cancer, (2) autotransplantation of frozen ovarian tissue in patients with *BRCA* mutations should be handled with caution due to significantly higher risks of developing ovarian cancer [41–44].

According to the aforementioned unique medical challenges as well as the responses from the 39 surveyed centers and their calculated oncofertility scores (Table 3 & Fig. 3), we suggest installing the following oncofertility programs for breast cancer as a best practice model (Table 4). **Before initiation of anticancer therapy**, cryopreservation of eggs or embryos should be attempted with a random-start protocol for controlled ovarian stimulation and using letrozole or tamoxifen to avoid high estradiol levels [45, 46]. Cryopreservation of ovarian tissue can be attempted especially when controlled ovarian stimulation is not feasible. In vitro maturation and further vitrification of oocytes retrieved in-vivo or ex-vivo from the extracted ovarian tissue (ovarian tissue oocytes in vitro maturation; OTO-IVM) could be attempted [47–49]. Artificial ovary technology is still experimental and cannot be relied upon alone as an effective oncofertility option. Although experimental, oocyte IVM and artificial ovary technology aim to provide safe alternatives to avoid future ovarian tissue autotransplantation and any potential risk of reintroducing malignant cells. **During anticancer therapy**, GnRH analog administration before and during chemotherapy should be considered for reducing the risk of POI but it should not be considered a stand-alone fertility preservation strategy. Fractionation of chemo- and radiotherapy could be attempted whenever deemed feasible by the oncologists. Neoadjuvant cytoprotective pharmacotherapy is still experimental and not yet clinically proven as an effective oncofertility option [50]. **After anticancer therapy,** fertility restoration may be achieved by frozen embryo transfer, or in vitro fertilization of stored oocytes. Patients with *BRCA* mutations could be advised to consider preimplantation genetic testing (PGT) during in vitro fertilization to avoid transmitting the mutation [51]. Autotransplantation of frozen ovarian tissue can be offered to restore fertility but it should be handled with caution in patients with *BRCA* mutations due to significantly higher risks of developing ovarian cancer. Proper ovarian tissue assessment in patients with *BRCA* mutations is mandatory to reduce the risk of reintroducing malignant cells with autotransplantation. For additional safety measures, it may be a possible option for patients with *BRCA* mutations to remove the transplanted ovarian tissue as well as the remaining ovary (if any) after childbearing is complete and at the time of an elective caesarian section. Stem cell reproductive technology may be promising in research settings but it is not yet clinically proven as an effective oncofertility option (Table 4).

After installation of these specific oncofertility programs for breast cancer, we encourage using the 'oncofertility score' as a prognostic tool to follow up on the development of these new oncofertility programs over time.

In cases where oncofertility options are rejected, contraindicated, infeasible, unsuccessful or unavailable, adoption and third-party reproduction, such as sperm, egg, and embryo donation and surrogacy can be offered as family building alternatives [11].

Limitations of Repro-Can-OPEN Study Part I & II included the small sample size (14 vs 25 surveyed centers with limited and optimum resource settings, respectively) making statistical significance difficult to attain, the empirical status of data collected on the availability and degree of utilization of oncofertility options, and lack of data on success rates of the oncofertility options due to absence of national registries for cancer and IVF treatments in many developing countries involved in the study [14, 15]. Despite challenges, many opportunities exist to improve oncofertility practice in limited resource settings and create potential

for the future including improved cancer survival rates and improved success rates of several oncofertility options as well as emergence of new promising technologies. The Oncofertility Consortium will continue to engage more stakeholders from the USA and abroad to help build a sustainable oncofertility core competency worldwide according to the Oncofertility Consortium Vision 2030 [52].

Conclusion

In our Repro-Can-OPEN Study Part I & II, the responses for breast cancer and their calculated oncofertility scores showed the following characteristics: (1) higher oncofertility scores in optimum resource settings than in limited resource settings especially for established options, (2) frequent utilization of egg freezing, embryo freezing, ovarian tissue freezing, GnRH analogs, and fractionation of chemo- and radiotherapy, (3) promising utilization of oocyte in vitro maturation (IVM), (4) rare utilization of neoadjuvant cytoprotective pharmacotherapy, artificial ovary, and stem cells reproductive technology as they are still in preclinical or early clinical research settings, (5) recognition that proper technical and ethical concerns should be considered when offering advanced and innovative oncofertility options. Although challenging, oncofertility teams working in limited resource settings should be encouraged and supported. Dissemination of our comparisons and recommendations will provide efficient oncofertility edification and modeling to oncofertility teams and related healthcare providers around the globe and help them offer the best care possible to their breast cancer patients.

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Declarations

Disclosure The authors have declared no conflicts of interest.

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