A SWOT Analysis of Oncofertility: Overcoming Resource Limitation to Fill an Ongoing Urgent Unmet Need

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Abstract

Resource wealth or absence defines access to many fields of science and medicine; the emerging field of oncofertility is one prime example of this resource and access dilemma. At the intersection of life and death, where life-limiting and life-producing events cross paths, the implicit contradictions of cancer and fertility have left men and women with limited choices, until recently. As the field of oncofertility expands, it was realized that many intellectual and practice based resource issues have equal or greater impact on access to care as insurance and reimbursement. Indeed, the contrasting emotions and expectations of practitioners and patients, together with a continued paucity of scientific knowledge about fertility in the cancer setting and the lack of clinical assessment of reproductive outcomes for adolescents and young adults, represent some of the boundary conditions to increase access to oncofertility. When these barriers are scaled up to the global setting, the need for advocacy and leadership from multiple organizations and individuals becomes urgent. To better understand this uniquely defined 'resource landscape', we conducted an analysis of the strengths, weaknesses, opportunities, and threats (SWOT) faced by global oncofertility—a SWOT analysis—to better understand the current state of the field and to create multimodal interventions that may provide a roadmap for the future of this discipline.

Keywords: fertility; cancer; global; access; oncofertility

Introduction

Discussions of low or no resource environments often focus on the global south or underserved areas of the United States, traditionally areas of relative poverty and poor access to medical care. Yet independent of geography, there are knowledge gaps, issues associated with the capacity to act, training and time constraints for the small healthcare and scientific workforce, limited infrastructure for medical research and practice, a paucity of scientific funding, provider reimbursement and patient insurance each of which contribute to the overall equation of 'access' and/or 'resource'. To increase access to care requires an evaluation of each of these contributors from three perspectives: fundamental reproductive science research, clinical research and practice, and patient/public health interests and goals. Analysis of these types of issues in the business community often involves an evaluation of the relative strengths and weaknesses of the programs or services as well as the opportunities and threats or challenges involved—called a SWOT analysis (Table 1). This kind of analysis has never been formally applied to the field of oncofertility, but may suggest new ways to approach access issues or advocate with medical societies or governments to improve care.

The topic of resources and access is particularly complicated when discussing oncofertility, a relatively new field that seeks to preserve the fertility of young patients with cancer [1]. The populations who might seek oncofertility care are male and female cancer patients younger than 40 years of age, including young adults, adolescents, and children. A cancer diagnosis is generally surprising and upsetting, but can be particularly so for very young children and their parents. Anticipating fertility needs for young people, especially for those in the youngest age group, can be even more challenging. The goal of this SWOT analysis is to outline the various factors that influence the amount of resources and relative availability of oncofertility care, and suggest ways in which these factors can be addressed to meet individual patient needs and expectations and ultimately improve fertility outcomes for young people with cancer. We highlight issues for basic scientists, clinicians, public health professionals, and policymakers working in this field. Each discipline has slightly different lenses through which they view the world; this analysis is therefore a starting point for discussion and is not intended to be comprehensive. It is anticipated that by identifying challenges beyond the well-discussed cost of IVF, we may be able to identify specific system-wide improvements in oncofertility care that will accelerate progress, such as the resolution of issues related to insurance and reimbursement.

Basic Reproductive Science

Knowledge Gaps: Impressive strides have been made in understanding ovarian follicle biology, spermatogenesis, and engineering of reproductive tissues, inspired by the urgent need of cancer patients who wish to protect their reproductive futures. Most importantly, the field has benefited from the collaboration of many traditional reproductive scientists with bioengineers and the introduction of engineering/regenerative medicine principles has led to a series of major advances in follicle biology [2, 3, 4]. For example, we now know that it is possible to grow mouse [2, 3], sheep [4], cow [5], rhesus [6] and non-human primate, and human [7, 8] ovarian follicles and produce mature oocytes entirely *in vitro*; these methods have been successfully applied to achieve live births in mouse [9, 10]. We know that pieces of human ovarian cortex can be cryopreserved and when thawed, and then transplanted back into a human recipient to result in live, healthy offspring [11-13]. Moreover, we know that spermatogonia can be isolated and propagated to achieve numbers that can support spermatogenesis after transplant [14]. Surgical methods to transplant the human uterus have also been developed, and human live births reported for ovarian and in uterus transplant patients [18]. These technical achievements were made possible by mechanistic studies in germ and somatic cell biology in the gonads and reproductive tract; however, we still need to understand more about the biology of these technologies and to improve the fidelity of each technique. Indeed, new opportunities for the field

include research into the mechanisms of germ cell development both *in vitro* and *in vivo* and programming of induced pluripotent stem cell (iPSC)-derived germ cells toward the germ cell lineage [15]; gene repair pathways that maintain genomic stability in the germ line; and how to assess egg and sperm quality after iatrogenic intervention or following long-term culture. Additional work is underway to make smarter biologic anti-cancer therapies that do not damage the germ cells, and to reduce the off-target effects of existing drugs [16, 17]. These are just a few areas of areas of basic research that will increase our stock of knowledge regarding ovarian, testicular and reproductive tract function; however, there is a significant gap in funding that supports this kind of research effort. The paucity of research funding is due in part to the fact that the oncofertility field lies at the intersection of funding agencies. For example, in the U.S., oncology research is funded by the National Cancer Institute (NCI) and reproductive science is funded by the National Institute of Child Health and Human Development (NICHD). Each Institute funds compelling research related to its primary mission, making it challenging to find support for research that lies at the periphery. The NICHD has directed funds toward an oncofertility portfolio and has championed this area of work, but more is needed to advance the mission of this cross-disciplinary field.

Capacity to Act/Workforce: Perhaps most threatening to the field of oncofertility is the paucity of students entering our field, making the pace of next-generation breakthroughs in oncofertility slower compared to other fields. Moreover, many of the problems that we seek to solve require input from multiple disciplines; for example, engineers to work with ovarian or testicular biologists, each of whom use terms or experimental paradigms that may be unfamiliar to the other. Thus, there is a need to create a shared language so that problems can be discussed and experimental details developed. This process requires an investment of time; in addition, there is a "coordination penalty" for doing interdisciplinary work that often leads to the loss of team members over time. Clinical colleagues also provide vitally important information to reproductive science researchers about the patient experience and gaps in care with contemporary tools or medicines. To engage clinicians in basic research and change clinical practice requires an understanding of conflicting priorities, workflow, and infrastructure to support patient care even while new research is underway. Multidisciplinary meetings like the annual Oncofertility Consortium Conference are critical to the progress of the field, as they bring groups together across disciplines, fields and professional setting in a venue that supports direct interaction and enables collaborative future work.

Knowledge Dissemination: One of the major obstacles to advances in the oncofertility field is the communication of the work itself. Basic scientists have relied primarily on the "paper-grant-paper" cycle to share their findings, but this methodology is not always be effective in providing other investigators with the necessary tools to replicate the work in their lab. The Oncofertility Consortium has addressed this issue in several ways. First the Consortium's webpage includes a repository for methods and videos for all of the technologies that have been created with NIH funding. This enables anyone to see the details of any method, including reagent vendors and catalog numbers (website). Second, we created the OC-SHARES (Oncofertility Consortium – Scientific Help Agreement for Research Endeavors) program. The goal of this program is to help the scientific community carry out basic oncofertility research by providing specific resources and tools. Currently, there are three resources available through OC-SHARES: 1) access to the NPC Human Research Tissue Repository, 2) use of the Stadie Riggs Tissue Slicer, and 3) request forms for Follicle Culture Kits. (http://oncofertility.northwestern.edu/oncofertility-consortium-scientific-help-agreement-research-endeavors-oc-shares-program). With access to the NPC tissue repository, investigators are able to ask fundamental questions about reproductive biology using rare human tissue samples. The tissue slicer is used to dissect the outer rim of the ovary and the program allows new oncofertility labs to practice with the equipment prior to purchasing their own. The

reagents in the Follicle Culture Kits help investigators learn the techniques needed for alginate-based encapsulated *in vitro* follicle growth (eIVFG) prior to investing in the reagents. To enhance the goal of oncofertility resource sharing, we also created iExperiment, a web-based resource that provides access to lab-based experts who demonstrate the methods used in eIVFG. Investigators can watch lab personnel isolate follicles in real time and ask questions. With each of these resources, the goal is to share widely all available oncofertility knowledge, techniques, and resources so that the time between discovery and translation to clinical care is shortened. While these are small steps, they have had an enormous impact on disseminating knowledge and accelerating the pace and quality of oncofertility research. Efforts to create new channels of communication between researchers must continue in order for advances in oncofertility techniques and technologies to be shared around the globe quickly and efficiently [18].

Clinical Oncofertility

Providing Personalized Risk Assessment: The availability of information about the infertility risk posed by cancer or a particular cancer treatment is of the utmost importance for making the decision to undergo fertility preservation treatment. This is especially true for women, as the available fertility preservation techniques are costly and require several days or weeks to be completed. Several cohort studies have demonstrated the reduction of female and male fertility after cancer treatment; the probability of having children was found to be reduced by half in the Scandinavian Cohort Study and the Childhood Cancer Survivors Study [19-21]. However, prospective studies are still lacking or are of inadequate size, and randomized controlled trials are difficult to implement for this population of patients due to the amount of time required to assess fertility status after treatment. The sample size in particular is a difficult hurdle to overcome due to the heterogeneity of patient age, tumor stage, and treatment. Prospective or observational studies must last several years or decades in order to evaluate whether a particular cancer type or a cancer treatment prematurely reduces the ovarian reserve and fertility potential. Patient selection may also be biased, as the patients who enroll in these studies are highly interested in fertility. Despite these challenges, efforts have been made to identify individual risk predictors of infertility risk among patients with cancer, most importantly, age in women and the type of cancer treatment. Pre-treatment evaluation of the ovarian reserve or sperm production is an important first step in estimating infertility risk, as reproductive function may already be compromised in patients with cancer. After cancer treatment, the recovery of ovarian or testicular function may occur months to years after radiation or chemotherapy. In men, semen analysis should be performed repeatedly in order to evaluate the recovery of sperm production, which can be delayed years after the treatment as the stem cells of the testicle reinitiate spermatogenesis. Although most studies have used amenorrhea as a surrogate marker for fertility loss in women, it is not an accurate marker; in fact, resumption of regular menses does not always signal intact fertility. New and more accurate markers of ovarian function are needed in order to counsel patients before and after cancer treatment.

Practice Management, Knowledge, and Access Barriers to Clinical Care: Oncofertility is a field that bridges reproductive science and oncology in an effort to preserve reproductive function for patients diagnosed with cancer. Achieving this goal requires a close collaboration of specialists involved in the treatment of cancer and infertility, who often have competing priorities. Discussions with patients about the possible risks posed by cancer and its treatment on fertility and the options for fertility preservation are necessarily complex—not only because multiple perspectives are in play but also because timing is crucial, particularly for patients with aggressive forms of cancer. This task can be particularly difficult in children with cancer, requiring practitioners to evaluate long-term infertility risks and offer appropriate fertility preservation techniques as soon as the urgent need for gonadotoxic treatment is established. Fertility preservation options for the youngest patients (immature gamete retrieval and

cryopreservation) remain largely experimental, and the availability of this procedure is limited to only a few centers. Indeed, one of the major threats to this field is the need to have professional societies in many disciplines embrace fertility in their setting –oncology, urology, allied health professionals, and reproductive endocrinologists (adult and pediatric) all need to be part of the equation.

Though the need for oncofertility and the collaboration between oncology and reproductive endocrinology is becoming globally recognized, with several scientific societies around the world establishing guidelines for fertility preservation in cancer patients [22, 23], there is still a gap in access—to knowledge, to the procedures themselves, and to support. To more fully address the issue of iatrogenic infertility after cancer treatment, it is essential to share information about oncofertility with individual cancer treatment centers, reproductive endocrinology and infertility practices, and infertility clinics. Updates in the field should be sent regularly to each of these stakeholders. Social media and traditional media must be engaged. Booklets and video resources should be widely distributed and available online. Mobile applications linking practitioners and patients to oncofertility care must be advertised extensively.

Inclusion of Psychological Support is Critical to Oncofertility Clinical Care Models: Psychological support during the oncofertility decision-making process is essential, especially for pediatric oncologic patients, who present very specific challenges [24]. They (or their parents) may be overwhelmed by the cancer diagnosis and focused on what is necessary to survive cancer rather than a discussion of possible future infertility. Even when a patient decides to undergo fertility preservation, they are more likely to select a quick "one-stop" strategy, such as ovarian tissue cryopreservation, that does not delay the initiation of cancer treatment and does not require the patient to be actively engaged in the fertility preservation treatment, as would be necessary for oocyte cryopreservation. This raises some concern, as in many cases patients may be choosing to undergo an experimental, but quicker, procedure when an established, but slower, one could be at least as effective and certainly less invasive. It is important that practices understand the value of specialized oncofertility support personnel and models that train psychologists in oncofertility navigation and counseling, to provide psychological and decision-making support to patients at single centers or between centers [25]. Building this capacity into oncofertility care is an important strategy that could be implemented on a macro (state, region, or country) scale.

Patient/Public Health

Access and Affordability: The cost of fertility preservation is well beyond the reach of most people; in the US, the average upfront cost of assisted reproductive technologies (ART) to cryopreserve oocytes is $9,200, plus annual storage fees of approximately $300, and $4,400 for thawing, fertilizing, and implanting the frozen eggs [26]. The primary reason for the underuse of ART, which has been available for the last 35 years around the world, is the cost of the treatment. Although insurance, reimbursement and specific cost issues vary in Europe, Asia, and North America, one of the major obstacles to the use of ART, whether in or outside the cancer setting, is the generally high cost of the procedures and medications. In many places in the world, including in countries in the global north like the US, infertility treatments are frequently not covered by health insurance [27]. In the global south, infertility treatments are commonly seen as luxury items, given the lack of resources and the need to prioritize basic, lifesaving healthcare [28]. In Portugal, considerable effort has been made to improve financial support programs for ART, and today, public ART centers offer fertility preservation for men and women, with 69% of medication costs covered by social security [29]. Country by country assessments of the costs of oncofertility are ongoing and will provide insight into future approaches to reduce cost as a barrier to access for patients with cancer. The ability to have genetic children is important to many

women and men throughout the world [28] and the World Health Organization considers infertility to be a global health issue [30]. The significance of genetic parenthood and the public health perspective are important to factor into the arguments for pursuing fertility preservation, particularly in resource limited environments. Ultimately costs and priorities are intertwined and should be considered in equal measure.

Public Awareness: While public awareness about oncofertility has increased dramatically in the last decade, there is still an overall lack of knowledge and understanding of the importance of fertility preservation in the cancer setting. The news media is a powerful tool for disseminating health-related news and it has played an important role in educating the public about oncofertility. However, awareness remains low among individuals who are less likely to be reached via the news media, those who are less educated, have lower health literacy, and are from lower socioeconomic backgrounds. Public awareness is the first step in creating public support for a given cause. Without widespread public support, is difficult for a movement to gain momentum and engender real change. One of the barriers preventing oncofertility from accumulating more public support is the perception that ART is an elective procedure that is not medically necessary. Yet, several professional medical organizations categorize infertility as a disease and there is substantial evidence demonstrating the physical, psychological, social, and economic impact of infertility and its treatment. Correcting this misperception and illustrating the health benefits of oncofertility, beyond fertility preservation, for patients with cancer is a major focus in the field.

Distinguishing between Oncofertility, Infertility, and Social Egg Freezing: Although oncofertility involves the same ART procedures used for infertility treatment and social egg freezing, oncofertility is specifically focused on the needs young patients with cancer whose future fertility is threatened by the cancer or its treatment. It is important to recognize the differences between oncofertility patients and patients with traditional infertility. Unlike patients who seek treatment for infertility, oncofertility patients have *anticipated* iatrogenic infertility that is directly related to their lifesaving cancer treatment. Unfortunately, these two categories are often conflated, leading to a similar exclusion of oncofertility procedures from insurance coverage as a form of infertility treatment [31]. Clearly classifying oncofertility as part of the cancer treatment plan would help establish the difference between oncofertility and infertility treatments, as well as improve access to and insurance coverage for ART procedures specifically in the oncofertility setting [32].

Many in the public also have difficulty distinguishing between the use of ART for fertility preservation in cancer patients, the use of ART for treating infertility, and the use of ART for fertility preservation to avoid age-related infertility—what has been called “social egg freezing” [33]. In the last few years, social egg freezing by women who want to delay childbearing has received a great deal of news media attention [34]. Given low health and science literacy rates among the public, people may not be able to immediately understand the different reasons for fertility preservation in cancer patients versus currently healthy women who are concerned about age-related infertility, especially since the same technologies are used in each setting. With the increasing demand for social egg freezing, there is the concern that the cost of fertility preservation will increase for all patients, including oncofertility patients. More work must be done to more clearly illustrate in plain language the differences in the use of ART in the oncofertility setting, for infertility, and in social egg freezing.

Summary and Next Steps

Oncofertility sits at the fulcrum of disciplines, and while it is viewed as essential to patients, it may be perceived as non-essential, niche or elective to funders and insurance groups or to clinical groups and government agencies. The field of oncofertility is driving the development of new fertility preservation technologies, many of which are urgently needed but remain experimental. The balance between perceptions about oncofertility for each stakeholder—patients, researchers, clinicians, funders, and policymakers—seem to shift constantly, resulting in professional and personal insecurities for practitioners and patients. Here we analyzed the existing strengths, weaknesses, opportunities and threats for the field of oncofertility from the perspectives of the basic scientist, the clinician and the public. The analysis shows a great need and a passion for the work with early adopters who are champions for the work. But funding limitations threaten ongoing basic research and clinical advances in all but a few centers and by a handful of investigators who are able to find alternative sources of support. Moreover, fertility is seen as a niche and not essential to many who are not directly affected by infertility or a cancer diagnosis. There are significant opportunities for basic scientists interested in developmental biology or soft tissue engineering, but many students are not aware of reproductive science research as a field when applying to graduate school. Indeed, graduate students and postdocs are more often lured to cancer biology labs based on the familiarity of the topic as well as the more stable paylines and diverse mix of public and private funders. Although we recognize the passion of first-generation oncofertility clinicians, many of whom are often forgoing payment for services provided to oncofertility patients, this is not a sustainable model for the growth of the field nor is it a systematic strategy for ensuring reimbursement and insurance coverage for oncofertility care. Finally, we know that the public is sympathetic with the issues associated with oncofertility patient needs, but more needs to be done to communicate the importance of oncofertility to all stakeholders, classifying it as a part of the cancer treatment plan and distinguishing the use of ART in the cancer setting as distinct from other settings that are perceived as elective. With the SWOT analysis in hand, work can be focused in each area to ensure that future resources are placed in areas that will maximize the outcomes.

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References

1. Woodruff TK. The Oncofertility Consortium--addressing fertility in young people with cancer. Nat Rev Clin Oncol. 2010;7(8):466-75. doi: 10.1038/nrclinonc.2010.81. PubMed PMID: 20498666; PubMed Central PMCID: PMCPMC3124936.
2. Kreeger PK, Fernandes NN, Woodruff TK, Shea LD. Regulation of mouse follicle development by follicle-stimulating hormone in a three-dimensional in vitro culture system is dependent on follicle stage and dose. Biol Reprod. 2005;73(5):942-50. doi: 10.1095/biolreprod.105.042390. PubMed PMID: 15987824; PubMed Central PMCID: PMCPMC2662519.
3. Desai N, Abdelhafez F, Calabro A, Falcone T. Three dimensional culture of fresh and vitrified mouse pre-antral follicles in a hyaluronan-based hydrogel: a preliminary investigation of a novel biomaterial for in vitro follicle maturation. Reprod Biol Endocrinol. 2012;10(1):29. doi: 10.1186/1477-7827-10-29. PubMed PMID: 22513305; PubMed Central PMCID: PMCPMC3474165.
4. Sadeghnia S, Akhondi MM, Hossein G, Mobini S, Hosseini L, Naderi MM, et al. Development of sheep primordial follicles encapsulated in alginate or in ovarian tissue in fresh and vitrified samples. Cryobiology. 2016;72(2):100-5. doi: 10.1016/j.cryobiol.2016.03.001. PubMed PMID: 26968252.
5. Sun J, Li X. Growth and antrum formation of bovine primary follicles in long-term culture in vitro. Reprod Biol. 2013;13(3):221-8. doi: 10.1016/j.repbio.2013.06.003. PubMed PMID: 24011193.
6. Xu J, Lawson MS, Yeoman RR, Pau KY, Barrett SL, Zelinski MB, et al. Secondary follicle growth and oocyte maturation during encapsulated three-dimensional culture in rhesus monkeys: effects of gonadotrophins, oxygen and fetuin. Hum Reprod. 2011;26(5):1061-72. doi: 10.1093/humrep/der049. PubMed PMID: 21362681; PubMed Central PMCID: PMCPMC3079470.
7. Wang TR, Yan J, Lu CL, Xia X, Yin TL, Zhi X, et al. Human single follicle growth in vitro from cryopreserved ovarian tissue after slow freezing or vitrification. Hum Reprod. 2016;31(4):763-73. doi: 10.1093/humrep/dew005. PubMed PMID: 26851603.
8. Xiao S, Zhang J, Romero MM, Smith KN, Shea LD, Woodruff TK. In vitro follicle growth supports human oocyte meiotic maturation. Sci Rep. 2015;5:17323. doi: 10.1038/srep17323. PubMed PMID: 26612176; PubMed Central PMCID: PMCPMC4661442.
9. Xu M, Kreeger PK, Shea LD, Woodruff TK. Tissue-engineered follicles produce live, fertile offspring. Tissue Eng. 2006;12(10):2739-46. doi: 10.1089/ten.2006.12.2739. PubMed PMID: 17518643; PubMed Central PMCID: PMCPMC2648391.
10. Kniazeva E, Hardy AN, Boukaidi SA, Woodruff TK, Jeruss JS, Shea LD. Primordial Follicle Transplantation within Designer Biomaterial Grafts Produce Live Births in a Mouse Infertility Model. Sci Rep. 2015;5:17709. doi: 10.1038/srep17709. PubMed PMID: 26633657; PubMed Central PMCID: PMCPMC4668556.
11. Donnez J, Dolmans MM, Diaz C, Pellicer A. Ovarian cortex transplantation: time to move on from experimental studies to open clinical application. Fertil Steril. 2015;104(5):1097-8. doi: 10.1016/j.fertnstert.2015.08.005. PubMed PMID: 26342246.
12. Donnez J, Squifflet J, Jadoul P, Demylle D, Cheron AC, Van Langendonckt A, et al. Pregnancy and live birth after autotransplantation of frozen-thawed ovarian tissue in a patient with metastatic disease undergoing chemotherapy and hematopoietic stem cell transplantation. Fertil Steril. 2011;95(5):1787 e1-4. doi: 10.1016/j.fertnstert.2010.11.041. PubMed PMID: 21145049.
13. Donnez J, Silber S, Andersen CY, Demeestere I, Piver P, Meirow D, et al. Children born after autotransplantation of cryopreserved ovarian tissue. a review of 13 live births. Ann Med. 2011;43(6):437-50. doi: 10.3109/07853890.2010.546807. PubMed PMID: 21226660.
14. Hermann BP, Sukhwani M, Winkler F, Pascarella JN, Peters KA, Sheng Y, et al. Spermatogonial stem cell

transplantation into rhesus testes regenerates spermatogenesis producing functional sperm. Cell stem cell. 2012;11(5):715-26. Epub 2012/11/06. doi: 10.1016/j.stem.2012.07.017. PubMed PMID: 23122294; PubMed Central PMCID: PMCPMC3580057.
15. Saitou M, Miyauchi H. Gametogenesis from Pluripotent Stem Cells. Cell stem cell. 2016;18(6):721-35. doi: 10.1016/j.stem.2016.05.001. PubMed PMID: 27257761.
16. Ahn RW, Barrett SL, Raja MR, Jozefik JK, Spaho L, Chen H, et al. Nano-encapsulation of arsenic trioxide enhances efficacy against murine lymphoma model while minimizing its impact on ovarian reserve in vitro and in vivo. PLoS One. 2013;8(3):e58491. Epub 2013/03/26. doi: 10.1371/journal.pone.0058491. PubMed PMID: 23526987; PubMed Central PMCID: PMCPMC3603968.
17. Kim SY, Cordeiro MH, Serna VA, Ebbert K, Butler LM, Sinha S, et al. Rescue of platinum-damaged oocytes from programmed cell death through inactivation of the p53 family signaling network. Cell Death Differ. 2013;20(8):987-97. Epub 2013/04/20. doi: 10.1038/cdd.2013.31. PubMed PMID: 23598363; PubMed Central PMCID: PMCPMC3705595.
18. Ataman LM, Rodrigues JK, Marinho RM, Caetano JP, Chehin MB, Alves da Motta EL, et al. Creating a Global Community of Practice for Oncofertility. J Glob Oncol. 2016;2(2):83-96. doi: 10.1200/JGO.2015.000307. PubMed PMID: 27284576; PubMed Central PMCID: PMCPMC4894337.
19. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2009;27(16):2677-85. doi: 10.1200/JCO.2008.20.1541. PubMed PMID: 19364965; PubMed Central PMCID: PMCPMC2690392.
20. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of male survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2010;28(2):332-9. doi: 10.1200/JCO.2009.24.9037. PubMed PMID: 19949008; PubMed Central PMCID: PMCPMC2815721.
21. Madanat LM, Malila N, Dyba T, Hakulinen T, Sankila R, Boice JD, Jr., et al. Probability of parenthood after early onset cancer: a population-based study. Int J Cancer. 2008;123(12):2891-8. doi: 10.1002/ijc.23842. PubMed PMID: 18798259; PubMed Central PMCID: PMCPMC2730156.
22. Lee SJ, Committee AFPG. Preservation of fertility in patients with cancer. N Engl J Med. 2009;360(25):2680; author reply 2-3. doi: 10.1056/NEJMc090614. PubMed PMID: 19535811.
23. Ethics Committee of American Society for Reproductive M. Fertility preservation and reproduction in patients facing gonadotoxic therapies: a committee opinion. Fertil Steril. 2013;100(5):1224-31. doi: 10.1016/j.fertnstert.2013.08.041. PubMed PMID: 24094423.
24. Yee S, Abrol K, McDonald M, Tonelli M, Liu KE. Addressing oncofertility needs: views of female cancer patients in fertility preservation. J Psychosoc Oncol. 2012;30(3):331-46. doi: 10.1080/07347332.2012.664257. PubMed PMID: 22571247.
25. Emanuel L, Johnson R, Taromino C. Adjusting to a Diagnosis of Cancer: Processes for Building Patient Capacity for Decision-Making. J Cancer Educ. 2016. doi: 10.1007/s13187-016-1008-3. PubMed PMID: 26960311.
26. Mesen TB, Mersereau JE, Kane JB, Steiner AZ. Optimal timing for elective egg freezing. Fertil Steril. 2015;103(6):1551-6 e1-4. doi: 10.1016/j.fertnstert.2015.03.002. PubMed PMID: 25881876; PubMed Central PMCID: PMCPMC4457646.
27. Quinn GP, Vadaparampil ST, McGowan Lowrey K, Eidson S, Knapp C, Bukulmez O. State laws and regulations addressing third-party reimbursement for infertility treatment: implications for cancer survivors. Fertil Steril. 2011;95(1):72-8. doi: 10.1016/j.fertnstert.2010.05.017. PubMed PMID: 20576264.
28. Fleetwood A, Campo-Engelstein L. The impact of infertility: why ART should be a higher priority for women in the global South. Cancer Treat Res. 2010;156:237-48. Epub 2010/09/03. doi: 10.1007/978-1-4419-6518-9_18. PubMed PMID: 20811838; PubMed Central PMCID: PMCPMC3071551.
29. Santos ATA, et al. Recomendações para a preservação do potencial reprodutivo no doente oncológico In: Oncologia SPD, editor. Revista Portuguesa De Oncologia2016.

30. World Health Organization. Infertility is a global public health issue. [November 2, 2016]. Available from: http://www.who.int/reproductivehealth/topics/infertility/perspective/en/.
31. Basco D, Campo-Engelstein L, Rodriguez S. Insuring against infertility: expanding state infertility mandates to include fertility preservation technology for cancer patients. J Law Med Ethics. 2010;38(4):832-9. Epub 2010/11/26. doi: 10.1111/j.1748-720X.2010.00536.x. PubMed PMID: 21105946; PubMed Central PMCID: PMCPMC3097090.
32. Campo-Engelstein L. Consistency in insurance coverage for iatrogenic conditions resulting from cancer treatment including fertility preservation. J Clin Oncol. 2010;28(8):1284-6. doi: 10.1200/JCO.2009.25.6883. PubMed PMID: 20142588; PubMed Central PMCID: PMCPMC2834493.
33. Baldwin K, Culley L, Hudson N, Mitchell H. Reproductive technology and the life course: current debates and research in social egg freezing. Hum Fertil (Camb). 2014;17(3):170-9. doi: 10.3109/14647273.2014.939723. PubMed PMID: 25093571.
34. Parker W, et al. Freezing fertility or freezing false hope? A content analysis of the portrayal of social egg freezing in the US print media. The International Network on Feminist Approaches to Bioethics World Congress 20162016.

Table

Figure 1

	Strengths	Weaknesses	Opportunities	Threats
Basic Science	Proven number of new discoveries in short period of time. Lives births. Capacity for global sharing of data and techniques; New Technology brought to reproductive science - bioengineering/regenerative medicine	Small field/limited visibility. Traditional bench research done in silos.	Interdisciplinary and translational approaches to challenging scientific problems. New discoveries. New mitigation strategies, iPS, reproductive tract transplants.	Lack of funding/lack of new researchers in STEM fields. Research driven by funding opportunities.
Clinical Medicine	Centers of Excellence - National Physicians Cooperative - shared protocols and linkages for professionals from providers, to allied health professions. Provides opportunities for training between groups.	Non-distributed model of care. Clinical guidelines and resources not integrated. Lack of patient navigators/oncofertility champions; lack of personalized fertility loss index at time of cancer diagnosis.	Next generation of fellows, residents, and medical students. Include in med school curriculum	Global heterogeneity in options. Professional societies must embrace.
Public Health	Interdisciplinary approach to two fields – oncology and reproduction/filling a clear unmet need	Assisted reproductive technologies are often not seen as a "real" public health problem/poor communication to public. Other more urgent needs in global south, world health crises (malaria, clean water, HIV/AIDS, etc).	Legitimize the importance of family formation for all types of patients/position oncofertility as a part of cancer treatment plan	Cost of assisted reproductive technologies/lack of insurance coverage for what is perceived to be an elective procedure
Overall	Fast assembly. Small field has capacity to adapt.	Fields of oncology and reproduction slow to integrate	Family building and endocrine health important to growing demographic of young cancer survivors. Increased awareness of options through media campaigns	Cost prohibitive. Religious constraints. Seen as niche - not essential.