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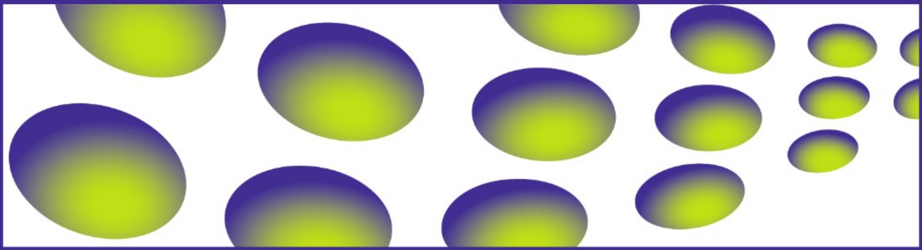

# Oncofertility

## Ethical, Legal, Social, and Medical Perspectives

Springer

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Lisa Campo-Engelstein · Sarah Rodriguez
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# Preface

Cancer affects millions of Americans annually. Men's lifetime risk of developing cancer for all sites is 50%; women's lifetime risk is just over 33% [1]. While generally cancer is perceived as a condition affecting the elderly, nearly 10% of those diagnosed are under the age of 45, which are typically considered prime child-bearing years [2]. Indeed, many of those diagnosed with cancer are still children. In 2006, an estimated 9,500 new cases of pediatric cancer were diagnosed in the United States [3]. Because of recent breakthroughs and more aggressive treatments, the survival rate of those diagnosed with childhood cancer has risen to almost 80% [4]. One estimate is that by 2010 one of every 250 adults will be a survivor of childhood cancer [5].

But while more aggressive treatments have meant more young people survive cancer, these treatments have also resulted in impaired fertility for some. Given the numbers of children and adults within their child-bearing years diagnosed with, treated for, and surviving cancer, the ability to biologically reproduce has become an important issue within oncology. Oncofertility has emerged as a way to address potential lost or impaired fertility in those with a history of cancer, with active biomedical research that is developing new ways to help those afflicted with cancer preserve their ability to have biological children [6].

Fertility concerns have begun to emerge as a quality of life issue important to patients. In one study of cancer survivors, 76% of those who were childless expressed a desire to have children in the future [7]. Impaired fertility as a result of cancer treatment has negative psychological as well as physical effects. The existing literature on women whose fertility was impaired as a result of cancer treatment reveals an intense psychological distress; for these women, "psychological distress may result from, not only the loss of the physical ability to conceive, but also a symbolic loss of the option or idea of fertility, regardless of whether this would have been acted upon or achievable" [8]. Studies on men have revealed similar levels of long-term distress over their impaired fertility as a result of cancer treatments [9].

The previous book, *Oncofertility: Fertility Preservation for Cancer Survivors*, primarily concentrated on the medical and technological aspects of oncofertility [10]. What differentiates this book from the first edited collection is the focus on perspectives from those outside of "hard" science. To move beyond oncofertility as a science and medical technology and begin to address the social, legal, and ethical ramifications of this emerging field, we must give voice to scholars from the humanities and social sciences to engage in an interdisciplinary discussion. This book, we hope, will begin such a discourse.

*Oncofertility: Ethical, Legal, Social, and Medical Perspectives* emerged from a robust summit that occurred in the summer of 2009, which brought together scholars from the humanities, social sciences, and the law, to examine the complex issues raised by recent developments in the field of oncofertility and to provide interdisciplinary perspectives to help shape the understanding and delivery of this new field. The book opens with some background information on the science and technology of oncofertility. The majority of this book addresses the ethical, legal, and social aspects of oncofertility and is divided into five sections: Historical and Legal Perspectives; Clinical and Theoretical Ethics; Religious Perspectives; Ramifications for Education and Economics; and Repercussions of Oncofertility for Patients and their Families. The final section is titled Health Care Provider Stories and Final Thoughts. Our first book highlighted patients' stories of facing cancer and potential infertility while being young. This book provides first person stories from the providers' side of the equation. In remarkably honest prose we are given insights into the impact oncofertility is having on the health care professionals drawn into this emerging field.

Both cancer and infertility play profound roles in American society beyond their existence as medical diagnoses. It is our hope that this book will be useful for people not only within the humanities and social sciences disciplines but also for those who are confronted with cancer and the possibility of impaired fertility and the medical practitioners within oncology and reproductive medicine who are at the front lines of this emerging field.

As with any book, there are many people to thank. We are grateful to Shauna Gardino, Jacqueline Kestler, and Bryan Breau for their organizational efforts and constructive criticism. We also wish to thank intern Daniel Basco for helping with necessary but tedious paperwork and Ehren Fourier for helping with the development logistics of this book. Finally, this book is an outcome of the summer humanities conference, and this conference could not have taken place without the help of interns Amanda Fleetwood, Andrew Russell, Kiran Screenivas, and Victor O'Halloran.

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# Part I
# The Science and Technology of Oncofertility

# Chapter 1
# Reproductive Health After Cancer

**Clarisa R. Gracia**

## Introduction

Recent diagnostic and therapeutic advances in oncology have led to greater survival rates in children and reproductive aged adults with malignancies. However, while cancer therapies improve long-term survival, such treatments can lead to a variety of reproductive problems including abnormal pubertal development, infertility, premature gonadal failure, and sexual dysfunction [1, 2]. As more children and young adults survive cancer and lead productive lives, these concerns are becoming increasingly important. However, the treatment of these conditions can be complicated both by the previous diagnosis of cancer and by comorbidities related to previous cancer therapy. Collaboration with a subspecialist in the area of reproductive endocrinology before and after cancer treatment can be helpful in managing the reproductive needs of cancer survivors [3]. Clinicians must be aware of the reproductive consequences of cancer therapies in order to anticipate and address the needs of cancer survivors so that they can lead healthy, fulfilled lives.

## Gonadotoxicity of Treatments

In the female, the ovary is particularly sensitive to the adverse effects of chemotherapy and radiation due to its finite number of un-renewable germ cells [4, 5]. A woman's reproductive life span is determined by the size of the follicular pool. Cancer treatments that cause follicular atresia and destruction of the follicular pool can lead to premature menopause and infertility [6, 7]. Alkylating agents and pelvic irradiation pose the greatest threat to ovarian function [6–11]. In addition, the uterine effects of pelvic irradiation may contribute to infertility and increase the risk of pregnancy loss [12]. Premature ovarian failure not only causes infertility but can

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lead to long-term health problems such as osteoporosis, cardiovascular disease, and sexual problems in women.

Cancer therapies also affect reproductive function in males. The mechanism for impaired spermatogenesis involves not only damage to the somatic cells that support spermatogenesis (Sertoli and Leydig cells) but also apoptosis of the germ cells themselves. Both chemotherapy, particularly alkylating agents and cisplatin, and testicular radiation pose a threat to future fertility. In addition, some surgical treatments for cancer can have an effect on transport of sperm and ejaculatory function [13]. In both males and females, cranial irradiation can have a profound effect on pubertal development and long-term reproductive function by disrupting the hypothalamic–pituitary–ovarian axis [14, 15].

## Fertility

The ability to lead full reproductive lives is very important to both female and male reproductive aged cancer survivors [16–18]. There is evidence that reproductive problems lead to substantial anxiety, which negatively affects quality of life in cancer survivors [19]. The reproductive risks of cancer therapies and fertility preservation options should be routinely discussed with patients prior to treatment. Consultation with a reproductive endocrinologist may be very helpful to provide adequate counseling regarding the reproductive consequences of cancer therapies and the risks and success rates of various fertility preservation strategies. A recent survey of cancer survivors reported that almost 30% of patients less than 50 years of age wanted more information about premature ovarian failure or health risks for their children, and a third of patients would have liked a fertility consultation before cancer treatment [20]. Semen cryopreservation remains the best option for fertility preservation in the post-pubertal male diagnosed with cancer. Fertility preservation in prepubertal boys remains problematic and is an active area of investigation. Extracting and cryopreserving spermatogonial stem cells from such boys in order to later autograft, xenograft, or mature in vitro are exciting and promising avenues of investigation [21]. In females, the most successful option for fertility preservation is emergency IVF and embryo banking prior to cancer therapy. However, this method is not appropriate for young women without a partner, prepubertal girls, or those who do not have time to delay lifesaving treatment. Other less effective and still experimental options for fertility preservation in cancer patients include oocyte and ovarian tissue cryopreservation [22]. Other options for minimizing the damaging effects of cancer treatments include oophoropexy or fertility-sparing cancer surgery [23]. In addition, co-administration of GnRH agonists may provide some protection against ovarian damage during chemotherapy, although prospective controlled trials are needed to establish any real benefit.

Given the potential of cancer therapies to cause reproductive problems, it is important to monitor a patient's reproductive function after cancer therapy. For males this includes an assessment of sexual function and a semen analysis. In women, it is important to monitor menstrual function, though hormonal contraception will mask any signs of ovarian failure. Importantly, menstrual function is not an adequate measure of fertility. Even women who maintain cyclic menses after therapy are at risk for early menopause, infertility, and long-term health problems related to early ovarian failure [7–9, 24–28]. Once clinical symptoms of ovarian dysfunction occur, such as irregular menses and vasomotor symptoms, pregnancy is usually not possible even with aggressive fertility treatments. Data suggest that measures of ovarian reserve, such as basal FSH, inhibin B, anti-mullerian hormone, and antral follicle counts, may be useful to monitor ovarian function in cancer survivors since they can reveal decreased ovarian reserve even in normally menstruating women [29, 30]. While such monitoring may be helpful particularly in patients who were unable to pursue fertility preservation techniques pretreatment and may benefit from fertility treatments or preservation post-treatment, these measures must be validated before routine use. In general, cancer survivors at risk for infertility should be counseled about pursuing pregnancy as soon as appropriate because the age-related decline in fertility may occur at an earlier age. In addition, cancer survivors experiencing delayed conception should be evaluated by a fertility specialist sooner than normally recommended (before 12 months of unprotected intercourse) given that such couples may have a shorter fertile window compared to couples without a history of cancer. Post-therapy options for having a family include fertility treatments including IVF, the use of donated gametes or embryos, or adoption.

Overall, data regarding the safety of pregnancy after cancer have been reassuring. Pregnancy does not appear to increase the risk of cancer recurrence in young patients, even for hormone sensitive tumors such as breast cancer [31]. While several studies of childhood cancer survivors have demonstrated an increased risk of low birthweight infants, primarily related to a history of pelvic irradiation [32, 33], cancer survivors who conceive at least 5 years following cancer treatment are not at increased risk of having a child with major congenital abnormalities [32, 34–36]. In addition, children of cancer survivors do not appear to be at higher risk of developing cancer themselves [37]. While these data are reassuring, further studies of large, current databases of cancer survivors are needed to provide more information for patient counseling. In general, the prenatal and obstetrical care of the cancer survivor should be multi-disciplinary, since the spectrum of medical complications resulting from cancer treatment benefits from diverse expertise. While many cancer survivors will be good candidates for carrying a pregnancy, others may be at high risk because of associated comorbidities. In such cases, a gestational carrier may be considered.

## Contraception

While cancer therapies can lead to infertility, a history of cancer does not necessarily mean that a patient is sterile. An unplanned pregnancy in the setting of a cancer diagnosis can be devastating, making treatment decisions more complex and putting the patient and pregnancy at high risk. Even after cancer treatment is completed, oncologists often recommend waiting at least 2 years before pursuing pregnancy. Many cancer survivors will never pursue pregnancy because of the perceived risk. Nonetheless, making a decision to continue or terminate an unplanned pregnancy in such cases can be very difficult. For these reasons, discussion of contraceptive options should be a priority after the diagnosis of cancer. Several factors should be considered when selecting among contraceptive options. The type of cancer may influence whether hormonal or nonhormonal agents are selected. For example, breast cancer is the most common malignancy in reproductive aged women in which hormonal contraception is contraindicated. A history of thromboembolic disease, significant liver dysfunction, or significant comorbidities may also make hormonal contraception a less desirable option. While barrier contraceptives are reasonable options for such patients, more effective methods include the nonhormonal intrauterine device (Paraguard) and permanent sterilization.

## Menopausal Symptoms

Premature ovarian failure can result in vasomotor symptoms and vaginal dryness. Other symptoms associated with menopause include sexual dysfunction, mood symptoms, and sleep disturbance. These symptoms can be very troublesome for patients and can significantly interfere with quality of life. Hormone replacement therapy in the form of traditional postmenopausal low-dose estrogen and progestin therapy or combine contraceptives are commonly prescribed to cancer survivors not only for the treatment of menopausal symptoms but also for the prevention of bone loss. There are no clear guidelines regarding hormone replacement therapy in this population since little data exist comparing the long-term safety and efficacy of various different forms of therapy in cancer survivors. Importantly, the results of large HRT trials such as the Women's Health Initiative cannot be generalized to the population of young cancer survivors with premature ovarian failure. Alternative therapies such as lifestyle modification, selective serotonin receptor inhibitors (SSRI), venlaxafine, and gabapentin may be useful for the management of vasomotor symptoms in breast cancer survivors and in other situations where estrogen is contraindicated [38]. Vaginal estrogens and lubricants are effective for the treatment of atrophic vaginitis and dyspareunia, and appear to be safe in patients who are not candidates for systemic estrogen therapy [39].

## Sexual Function

Overall, at least 20% of cancer survivors experience sexual dysfunction, and a higher proportion of survivors with a history of colorectal, prostate, gynecological, breast, and bladder cancer [1]. It appears that all phases of the sexual response cycle are affected by cancer. However, men are most likely to experience erectile dysfunction and women experience decreased libido and vaginal dryness. Impaired body image after cancer may be an important factor influencing sexual function as well. Sexual rehabilitation after cancer may significantly improve quality of life [40]. Moreover, there is evidence that even adolescent and young adult cancer survivors benefit from education and support surrounding issues of sexual development and function, body image, fertility, prevention of sexually transmitted disease, and unwanted pregnancy. In one small pilot study, such an intervention increased cancer-specific knowledge regarding sexual issues, improved body image, lessened anxiety about sexual relationships, and decreased psychological distress [41].

As the number of young cancer survivors continues to increase, it is important for clinicians to be aware of the reproductive risks and concerns specific to this population. This chapter has reviewed some of the main reproductive consequences experienced by cancer survivors and provides guidance regarding the management of these conditions.

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# Chapter 2
# Designing Follicle–Environment Interactions with Biomaterials

**Rachel M. Smith, Teresa K. Woodruff, and Lonnie D. Shea**

## Introduction

The recruitment, selection, and ovulation of follicles, termed folliculogenesis, result from a complex set of signals that are exchanged between the follicle and its environment. These interactions include circulating hormones, extracellular matrix (ECM) components, and mechanical signaling. The ovarian environment is highly dynamic, which has been commonly characterized by the cyclic changes in endocrine factors. Disruption of this dynamic interplay between the follicle and its environment, which can result from environmental toxins, disease, or disease therapies, underlies many causes of infertility. Although the significance of endocrine factors has been widely recognized, numerous other aspects of the ovarian environment are increasingly being recognized for their role in regulating folliculogenesis. Identifying the environmental mechanisms that regulate follicle development is essential for creating novel strategies to preserve fertility.

The field of biomaterials and regenerative medicine has been developing the tools to create tunable microenvironments, which can be employed to investigate the basic biology of tissue development and also to develop therapeutic strategies for tissue loss or organ failure. Biomaterials have been widely used for in vitro cell culture to provide support for cell growth and attachment within a three-dimensional architecture in the absence of the endogenous tissue. Many properties of tissue can be mimicked with biomaterials such as the mechanical strength, or the presentation or sequestration of biological signals. The potential of biomaterials to address significant clinical problems is exemplified by the biomaterial-based culture of urothelial and smooth muscle cells, which was employed to create a functional synthetic bladder [1]. The successful translation of this system from an animal model to human clinical use was reported in 2006 [2]. The success of this engineered bladder has

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motivated its methodology to be used in other areas of regenerative medicine. Using a similar method, an artificial vagina was recently developed for a rabbit model that was integrated into the host tissue 6 months after vaginal replacement [3].

The need for fertility preservation for females facing cancer therapies provides an opportunity for biomaterials use in the field of reproductive biology [4–6]. Patients can elect to undergo hormonal stimulation prior to cancer treatment, but the feasibility of this option is dependent upon many variables, such as the patient's age, the urgency of the cancer treatment, and the availability of a sperm donor. In the future, patients may be able to opt to bank a portion of an ovary for use with ovarian tissue transplantation or in vitro culture to preserve their fertility. The culture option, the focus of this chapter, requires a culture system for in vitro folliculogenesis that produces oocytes that are viable for in vitro maturation (IVM) and subsequent in vitro fertilization (IVF). It has been demonstrated that the biomaterial alginate, in the form of a hydrogel, can provide a permissive environment for the folliculogenesis of a two-layer secondary follicle, and the cultured oocyte can be fertilized to obtain a live birth in mice [7]. The recent successful growth of human two-layer secondary follicles into antral follicles in vitro [8] provides theoretical and practical basis to support the translation of this system to a clinical application. Recapitulating the native ovarian environment within an in vitro culture system is generally viewed as necessary to obtain the highest quality oocytes. Light micrographs typical of three stages of murine folliculogenesis in alginate culture are shown in Fig. 2.1. Further development and characterization of in vitro follicle culture is needed for translating this system from mice to the clinic.

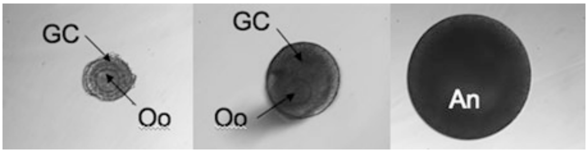

**Fig. 2.1** Stages of murine folliculogenesis during in vitro follicle culture. All follicles shown are encapsulated within alginate. A two-layered secondary follicle (*left*) is the most immature follicle that can be cultured to obtain a live birth in vitro. A multilayer secondary follicle (*center*) and antral follicle (*right*) are the subsequent stages of folliculogenesis. Both two-layered and multilayered secondary follicles are referred to as pre-antral. The oocyte (Oo), granulosa cells (GC), and antrum (An) are labeled. Note that the oocyte is obscured in the antral follicle by the multiple layers of granulosa cells

The potential of biomaterials in reproductive biology is not limited to clinical applications and can be employed to investigate the mechanisms of follicle development. The goal of this chapter is to describe follicular interactions with their environment and the rational design of biomaterials to mimic and investigate those interactions. Biomaterial-based culture systems can be an enabling tool to investigate the spatio-temporal changes that occur within the follicle and the surrounding tissue. Follicle–environment interactions in this chapter are categorized as (i) extraovarian interactions and (ii) interactions between a follicle and the ovarian tissue.

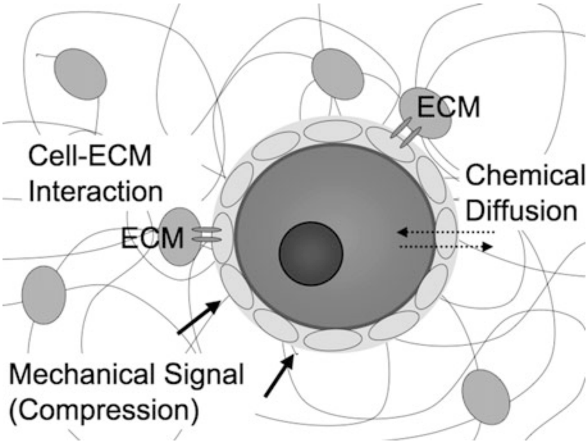

**Fig. 2.2** Interactions between the follicle and its environment in vitro. A representation of a follicle within a hydrogel matrix is shown. Extraovarian interactions are incorporated into an in vitro culture through diffusible factors. The physical properties of a hydrogel will impact how quickly diffusion occurs. Hydrogels mimic the role of ovarian tissue by presenting extracellular matrix (ECM) proteins, through which receptors on the plasma membrane can interact with the matrix. Mechanical signals are also presented by the hydrogel through a compressive force from the elastic rigidity of the matrix

These interactions are summarized in Fig. 2.2. This chapter reviews the recent advances in the design of biomaterials for follicle culture, and we refer to other reports for a more thorough history [9].

## Extraovarian Interactions

The ovary receives numerous inputs from the systematic circulation, which we refer to here as *extraovarian interactions.* The systematic circulation is responsible for transporting biological signals, such as hormones, nutrients, waste, toxins, and oxygen. In mimicking the environment within the ovary, these factors are typically provided by addition to the cell culture media and are transported through the culture environment by diffusion. In particular, cells cultured within synthetic hydrogels recapitulate the 3D architecture observed in vivo; however, this matrix and the formation of the multi-cellular structure of the follicle can impose transport limitations with the potential to affect a range of cellular processes, which are discussed further below. Additionally, in vitro cultures can allow a molecule of interest to be investigated for its effects, which can identify the mechanisms of action that underlies in vivo biology. For instance, there has been an increasing concern on the effects of industrial chemicals, such as bisphenol A (BPA), on human fertility. The use of in vitro follicle culture as a bioassay [10, 11] provides a unique platform to investigate the mechanisms by which diffusible factors that can end up in the systemic circulation, such as hormones, nutrients, and environmental toxins, impact follicle growth and development. These systems have implications in the fertility of humans, livestock, and endangered species.

## *Introduction to Mass Transport in Hydrogels*

A hydrogel is a highly water-swollen polymer network. Many hydrophilic polymers, such as fibrin, chitosan, and alginate will form hydrogels if they are cross-linked into a network. For instance, alginate is a naturally occurring polysaccharide that is composed of mannuronic acid and guluronic acid. When a divalent cation, such as calcium, is added to a solution of alginate, the anionic (carboxylic) group on two different residues of guluronic acid will form an electrostatic crosslink with a single calcium ion. The crosslinking between polymers will create a network, which creates the solid-like structure of the gel. This section provides a brief overview of hydrogels: what they are, how they form, and the influence their physical properties have on diffusible factors during cell culture.

Unlike an in vivo setting where there is an extensive vascular system to transport nutrients and waste efficiently, all transport in vitro must rely on diffusion. Direct interaction between a follicle and the surrounding biomaterial (such as ECM–integrin interactions) will be considered in later sections. Transport through the hydrogel network is determined largely by the hydrogel architecture and its chemistry. The architecture of the hydrogel's network, as well as its chemical composition, is critical for providing a permissive environment for cell culture because it will determine the rate at which nutrient and waste move between the culture media and the encapsulated cells. The structure of the network can depend upon many conditions, such as the type(s) of polymers present, the concentration of the polymer, the molecular weight of the polymer, and the crosslinking conditions.

Two important properties of the hydrogel architecture that are influenced by polymer concentration and molecular weight are pore size and tortuosity. Any supplement provided in the culture media must diffuse into the hydrogel, as well as navigate from the surface of the hydrogel to the encapsulated cells. The time it takes for a solute to travel this route will be largely determined by the pore size and tortuosity. If the pore size is small, relative to the diffusing molecule, there may significant mass transport limitations. Consider bovine serum albumin (BSA), which has a Stokes radius of 3.6 nm [12], in 1.5% versus 3% alginate, which has a pore size of 17 and 15 nm, respectively [13]. In comparison to free diffusion in water, the diffusion rate of BSA in 1.5 and 3.0% alginate hydrogels is decreased by 27- and 48-fold, respectively [13]. Table 2.1 lists the diffusion coefficients for several solutes relevant to cell culture. Follicle-stimulating hormone (FSH) is another essential soluble factor for follicle culture [14]. The diffusion of FSH, a large protein hormone with a molecular weight of $3 \times 10^4$, has not been directly studied, but there is experimental evidence that the protein can be transported through the hydrogel; however, its rate of diffusion is hindered by alginate [15].

**Table 2.1** Diffusion coefficients (D) of different solutes in alginate hydrogels. The molecular weight of the alginate polymers was 350 kD and the hydrogel was crosslinked for 5 min in a calcium solution [18]

| Solute | Stoke's radius (nm) [10] | D, water ($cm^2/s$) [10] | D, 1.5% alginate ($cm^2/s$) [18] | D, 3.0% alginate ($cm^2/s$) [18] |
|---|---|---|---|---|
| Oxygen | 0.15[a] | $2.7 \times 10^{-5}$ | $1.4 \times 10^{-5}$ | $1.2 \times 10^{-5}$ |
| Glucose | 0.35 | $9.2 \times 10^{-6}$ | $6.0 \times 10^{-6}$ | $6.2 \times 10^{-6}$ |
| BSA | 3.6 | $9.6 \times 10^{-7}$ | $3.5 \times 10^{-8}$ | $2.0 \times 10^{-8}$ |

[a] van der Waals radius

Even though oxygen is small relative to the pore size, its diffusion is still decreased in alginate (Table 2.1); thus, not all diffusion effects can be explained by pore size. The cause of the slower diffusion rate is likely due to the tortuosity of the hydrogel's architecture [13]. The tortuosity of a material describes how tortuous or "windy" of a path the solute must take in the hydrogel. The concept of tortuosity is exploited in size-exclusion chromatography techniques where smaller molecules elute from a packed column after larger molecules because there are more pores that a small molecule can fit into; thus, smaller molecules have a more tortuous path through the column. Note that the decrease in the diffusion coefficient of oxygen is relatively small in alginate, approximately twofold, but this example illustrates that the diffusion of a solute through a hydrogel is more complex than the relative size between the diffusing solute and the pores of the hydrogel.

Cross-linking conditions, such as duration of cross-linking and the concentration of cross-linking agent, will play an important role in the formation of the hydrogel architecture, and thus the transport of solutes as well. For instance, the structure of fibrin-alginate interpenetrating networks (FA-IPN), which has been successfully used for follicle culture [16], depends upon thrombin concentration. Thrombin is a serine protease that actives factor XIII, a transglutaminase, which covalently cross-links glutamine and lysine residues on fibrinogen fibers. If fibrin is cross-linked with a high concentration of thrombin (500 IU/mL), the resulting network has thin, dense fibers relative to a network cross-linked with 5 IU/mL thrombin [16]. A denser matrix would be more likely to impair the diffusion of solutes through the scaffold. Therefore, many factors contribute to overall transport properties of hydrogels that are used for follicle encapsulation. Understanding these properties is essential for developing the follicle culture system, as well as proper interpretation of experimental results.

## Ovarian Tissue Interactions

The ovarian tissue, which is composed primarily of extracellular matrix (ECM) and stromal cells, directly interacts with a follicle through biological and mechanical signaling. The ECM is a complex composite of fibrous proteins and polysaccharides and is present in all tissues in the body. There are structural elements called "binding motifs" on the ECM components that are recognized by receptors on the plasma membrane of cells. Integrins are the primary family of proteins responsible for ECM recognition and binding, and are ubiquitous across species and cell lines. Replicating the role of the ECM with biomaterials provides researchers with a tool to create artificial tissue for clinical therapies and in vitro cell culture, and will be the focus of this section. Many cellular and biological processes that occur in vivo, such as migration, differentiation, and angiogenesis, are supported by biomaterials that mimic the biological activity of the ECM. The influence of mechanical signaling on cells by the surrounding tissue can be as significant as the presence of a biological signal, such as a growth factor. For example, if stem cells are cultured on a gel with a high, intermediate, and low modulus, they will differentiate into bone, muscle and neural cells, respectively, which is representative of their native tissue [17]. In general, a guiding principle of tissue engineering is to create materials with mechanical properties similar to the native tissue.

A key aspect of a biomaterial is its bioactivity, which typically entails incorporating factors that will promote tissue growth while excluding factors that may be inhibitory. Two aspects of bioactivity that are incorporated into a biomaterial are the support of cell adhesion and the presentation of growth factors. Cell adhesion can be supported by hydrogels in at least three ways: (i) using natural polymers with intrinsic biological activity, (ii) chemically modifying a material not otherwise recognized by the encapsulated cells with biologically active factors, and (iii) create a mixture of natural and synthetic materials, such as an interpenetrating network. Polymers with intrinsic biological activity are generally components of the extracellular matrix found in native tissue, such as fibrin and collagen. Inert materials, such as alginate, chitosan, and PEG, are not recognized by mammalian cells, but can still enhance cell culture by providing a 3D environment for cell development. Chemical modification of inert materials, such as the covalent attachment of integrin binding sequences or growth factors, allows for precise control of interactions between the biomaterial and the cultured cells. In regards to growth factors, these materials are being modified to support binding and/or release of growth factors, which can stimulate responses by cells entrapped within the gel.

## *Designer Environments for Follicle Culture*

Creating an artificial environment for follicle development that is representative of the native tissue presents a unique engineering challenge because the ECM of the ovarian tissue exhibits spatio-temporal dynamics with respect to stage of the folliculogenesis, particularly in the basal lamina surrounding the granulosa cells [18–20]. Non-degradable follicle environments, such as encapsulation within alginate, have been shown to provide a permissive environment for follicle development and fertilizable oocytes in both 3D [7] and 2D environments [21]. Results with alginate have led to the development of a degradable cell-responsive matrix for follicle culture that is based on a fibrin-alginate interpenetrating network, which greatly enhanced oocyte quality relative to the alginate culture system [16]. Synthetic environments with tunable properties provides researchers with a tool to isolate the mechanisms underlying follicle–tissue interactions to shed light on the basic biology of follicle development as well as provide insight into how to improve existing in vitro culture conditions.

## Modification of Synthetic Biomaterials for Follicle Culture

Integrin binding motifs and growth factors are frequently attached to synthetic biomaterials to provide bioactivity. A commonly used integrin-binding motif is the peptide sequence RGD (arginine–glycine–aspartic acid). The RGD motif is found on most ECM proteins, including laminin, collagen, and fibronectin. The presence of an RGD peptide on an otherwise inert hydrogel will support a variety of cell processes such as attachment, migration [22], proliferation, and differentiation [23]. Growth factors can similarly be presented from the matrix. Growth factors are not covalently attached to the ECM in vivo; however, the ECM does sequester growth factors through relatively weak interactions. Growth factors have been directly conjugated to the matrix, though a key consideration is that the chemistry for attachment must not affect the activity of the protein. Alternatively, hydrogels have been modified with motifs, such as heparin [24], that support the reversible binding of growth factors. The response of the cell to an immobilized growth factor may differ from the response to a soluble growth factor. For example, an immobilized growth factor may be more potent than a soluble growth factor, meaning that a lower concentration of an immobilized growth factor will have the same influence as a greater concentration of soluble growth factor.

The immobilization of growth factors and integrin binding motifs are enabling tools to precisely control the environment of the cell that would not otherwise be feasible. In a landmark study, it was demonstrated that endothelial cell shape controlled apoptosis, and cells that were able to spread out over a larger surface area had a significantly lower rate of apoptosis [25]. In addition to controlling the size of the domain, gradients of biological factors can be imprinted on a material, which has been employed to investigate the chemotactic response of cells. Chemotaxis is the biased migration of a cell from a low to a high concentration of a chemical agent, as opposed to a random walk if there is no biasing force. A gradient will be present anywhere that there is a chemical source (a cell secreting a biological factor) and a sink (the rest of the tissue). A well-characterized chemotactic response in reproductive biology is the directed movement of sperm toward the oocyte for fertilization. These chemotactic factors have been shown to accumulate in the follicular fluid of the follicle [26]. Although not currently used for follicle culture, gradients have been extensively studied for their use in other disciplines in regenerative medicine, particularly for nerve regeneration and the chemotactic response of axon growth cones.

The application of synthetic matrices to support follicle development has been a recent advance in the field. Inclusion of an RGD peptide on a hydrogel can influence murine [27] and ovine [28] granulosa cells cultured in a 2D environment. Murine granulosa cells cultured on RGD-modified alginate have increased survival and proliferation, as well as a different morphology, in comparison to alginate alone. Hormone secretion was also influenced by the attachment of an RGD sequence and was dependent on the density of the RGD peptide [27]. The success of RGD peptides influencing granulosa cell function motivated their application to follicle culture. Alginate modified with an RGD-binding motif significantly increased the growth of two-layer secondary follicles in comparison to alginate alone, and meiotic competency rates were improved as well [29]. Steroid release was also significantly different in the presence or absence of RGD peptides. The presence of RGD led to an increase in progesterone secretion and a decrease in estradiol and inhibin A secretion [29]. These results suggest that integrin interaction with the environment can enhance the development of follicles in vitro.

## Incorporation of Natural Biomaterials for Follicle Culture

Polymers that are isolated from the ECM of tissue, such as collagen and fibrin, are intrinsically bioactive. There are several sub-types of collagen, which gives tissues, such as connective tissue and muscle tissue, its characteristic elastic strength. Fibrin is the ECM protein responsible for blood clotting and is formed via enzymatic crosslinking. Both fibrin and collagen have been used extensively in the field of biomaterials for creating artificial tissues. As mentioned previously, these materials can be formed into a single-component hydrogel, or they can be blended with another polymer to create an interpenetrating network (IPN).

Collagen was one of the first biomaterials used for 3D in vitro follicle culture [30]. In this study, which used hydrogels composed only of collagen, follicles survived in vitro for 2 weeks and multilayered follicles were formed, but no follicles proceeded to the antral stage [30]. More recently, buffalo pre-antral follicles encapsulated in collagen have been shown to develop an antrum [31]. Follicles have also been encapsulated in fibrin. However, enzymes secreted by the encapsulated follicle rapidly degraded the fibrin, and the 3D integrity of the follicle architecture was lost when it fell to the bottom of the culture plate [16]. Thus, fibrin alone cannot support 3D in vitro culture of follicles. Blends of an ECM component, either laminin, or fibrinogen, or collagen I, or collagen IV and alginate were used to study follicle–ECM interactions [29]. Interestingly, the influence of the ECM component on follicle development depended on the stage of the follicle upon encapsulation. For instance, relative to follicle growth in pure alginate, collagen IV enhanced the survival of two-layer secondary follicles, but diminished the survival of multilayer follicles [29]. Optimization of dynamic, synthetic materials has the potential to enhance follicle culture, and to understand how the follicle interacts with the ovarian tissue in vivo.

More recently, a fibrin-alginate interpenetrating network (FA-IPN) was developed for in vitro growth of follicles in order to combine the bioactive properties of fibrin, while maintaining the 3D structure of the follicle [16]. An IPN is a blend of at least two polymers where at least one polymer is crosslinked in the presence of another [32]. This results in an entangled network that gives the IPN its name. IPNs can be advantageous because desirable properties, such as bioactivity and degradability, of more than one material can be utilized in a single system. In the case of the FA-IPN, alginate maintains the structure of the follicle because it is not degradable, and the fibrin provides bioactivity.

## *Interactions with the Mechanical Environment*

Engineering synthetic tissues for cell culture requires an understanding of the biological cues presented by the system, and the mechanical signals that are presented as well. The mechanism by which cells translate a mechanical signal to a biological one, a process known as *mechanotransduction*, is currently under investigation. Although not completely understood, mechanotransduction is exhibited by many cell types, and disruptions in the mechanical environment of tissues is associated with disease phenotypes, as is the case with arthrosclerosis, where hardening of the arteries is observed. Tissue rigidity is also thought to play a role in the progression of breast cancer [33, 34], which is often detected physically through palpation.

Polycystic ovarian syndrome (PCOS) is a common cause of infertility in young women. It has been suggested that a change in the mechanical environment of developing follicles contributes to the anovulation observed in patients with PCOS [35]. This hypothesis is supported by the observation that immature follicles cultured in a more rigid 3D environment are less able to proceed through folliculogenesis to the antral stage [35, 36]. In a proteomic comparison of polycystic ovaries (PCOs) and normal ovaries [37], alterations in protein expression were observed that could lead to accumulation of fibrin and collagen. Specifically, an increase in the level of fibrinogen precursors was present, which could potentially impair the fibrinolysis pathway in the PCOs. Additionally, both a collagen precursor and a chaperone protein (HSP47), the latter of which stabilizes pre-collagen and aids in the assembly of collagen fibers [38], had increased expression in the PCOs [37]. An increase in the deposition of ECM from these observed changes in protein expression could lead to hardening of the ovarian tissue. Most studies investigating mechanotransduction have used 2D culture conditions because the physical properties of the system can be independently manipulated more easily. However, if cultured in a 2D environment, granulosa cells will detach and migrate from the developing oocyte. Thus, an in vitro system for folliculogenesis presents a novel system in which to study basic biological questions governing interactions between cells and a 3D mechanical environment.

The mechanical properties of the environment can determine if the environment is permissive for follicle development [35, 36]. As a follicle develops in a 3D environment in vitro, its diameter increases, and the surrounding hydrogel will exert a compressive force on the follicle in response to the expansion. The compressive force is dependent upon the elastic strength of the hydrogel, as well as the change in size of the follicle. The volume of the hydrogel that is displaced by the developing follicle increases as $r^3$, where $r$ is the radius of the follicle, but the surface area that is acted on by the compressive force increases only as $r^2$. During murine folliculogenesis, the approximate changes in dimensions are an 11-fold increase in surface area and 37-fold increase in volume, starting from a two-layered secondary size of $\sim$120 μm and ending at an antral size of $\sim$400 μm. To date, researchers have been successful in creating systems that are permissive for follicles at this stage of development. In primates, the change in volume relative to surface area during folliculogenesis is much more significant than in murine follicles, which may present a challenge in translating a murine to a human follicle culture system that could be used clinically. Specifically, a human follicle, if cultured from a two-layered secondary follicle ($\sim$120 μm) to a large antral follicle ($\sim$20 mm), would have a 28,000-fold increase in surface area and a 4.7 million fold increase in volume. Therefore, the stress profile in a human follicle culture may be significantly different than a murine follicle culture, and this may contribute to the reason why materials optimized for murine follicle culture remain sub-optimal in human follicle culture. Creating a permissive in vitro system for human follicle growth that has clinical applications for fertility preservation must be able to reproducibly yield large antral follicles, so that IVM and IVF could be successfully administered at a reasonable success rate.

Characterizing the physical properties of biomaterials is essential to investigating the influence of the mechanical environment on cells created by an in vitro culture system, as well as to determine the mechanics of healthy and diseased tissue. Materials are characterized using techniques from rheology, which is the study of flow phenomenon, and a rheometer is the instrument commonly used to determine the mechanical properties of a material. Most biomaterials, both synthetic and natural, are polymers, and thus exhibit properties of both a liquid and a solid – a phenomenon known as viscoelasticity due to the viscous nature of liquids and the elastic nature of solids. The underlying cause of the viscoelasticity of polymeric materials is their chain length. As the chains of polymers become entangled, their movement becomes increasingly restricted. A liquid material that is entangled at the molecular level cannot flow as freely as a non-polymeric liquid, which results in an elastic response, as opposed to a viscous response. Therefore, parameters such as the polymer concentration, the molecular weight, and the degree of polymer branching will increase chain entanglements, and thus the mechanical strength of the material. Although viscoelastic properties are beneficial for tissue engineering, they are difficult to characterize rigorously because the viscosity and the modulus (the measure of elasticity) are dependent upon the time scale of the experiment. For instance, the elastic and viscous response of a material can be separated into the storage (i.e., a solid stores and remembers its original shape) and loss (i.e., a liquid losses and forgets its original shape) modulus, respectively, in *small amplitude oscillatory shear* (SAOS) experiments, which is a common technique used in rheometry to study viscoelasticity. However, the measured moduli are dependent upon the frequency of the oscillations, which contrasts with a material such as glycerol, which has a viscosity independent of frequency. A schematic of a rheometer for SAOS is shown in Fig. 2.3.

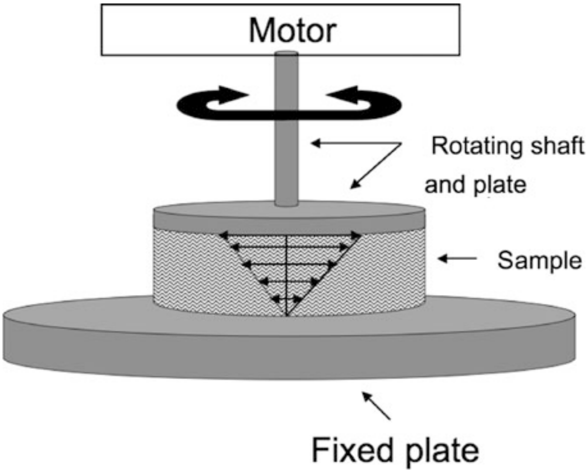

**Fig. 2.3** Rheometer schematic for small amplitude oscillatory shear. A motor oscillates a rotating shaft and plate at varying frequencies at a fixed strain amplitude. An idealized velocity profile within the sample is shown. In response to the applied strain, the material will exert a torque on the rheometer. If the sample is viscoelastic, the torque will be dependent on the applied frequency, as will the phase angle between the torque and the strain. The torque and phase angle are the only measurements needed to calculate the storage and loss modulus of the sample

The initial study to indicate an impact of environmental rigidity on follicle growth in vitro used varying concentrations of alginate to control the hydrogel rigidity [36]. Increasing the concentration of the polymer in solution is a well-known method of increasing the modulus of a hydrogel. A 0.25% alginate hydrogel, which creates relatively soft beads, was more permissive for follicle growth than the other concentrations tested (0.5, 1, and 1.5%). The 0.25% hydrogel improved growth, increased steroidogenesis of estradiol and androstenedione, and had a higher yield of meiotically competent oocytes. Varying the solids content of a hydrogel is a simple method to modulate the mechanics; however, as previously discussed, the solids content can also impact the transport of solutes due to a changing pore size.

A subsequent study attempted to isolate the impact of the mechanical properties from the transport effects. Chemical modification is an alternative means to control the mechanical properties of alginate hydrogels [39]. By using an irradiation source or an oxidizing agent, the individual polymer chains can be broken to reduce the average molecular weight, which will decrease the rigidity of the crosslinked hydrogel at a fixed solids concentration. Hydrogels with a decreased elastic modulus, created either through irradiation or through oxidation of the alginate, led to improved follicle growth. Furthermore, follicles encapsulated in materials with a lower solids content had higher rates of antrum formation than follicles encapsulated in materials with a higher solids content, but a similar gel stiffness. Alginate hydrogels formed with a lower solids content have a larger pore size, suggesting that transport of diffusible factors is significant in follicle culture even at low concentrations of alginate. Interestingly, the antrum has been hypothesized as a means for the follicle to overcome transport limitations as the diameter of follicle rapidly expands during the latter stages of folliculogenesis [40, 41].

The mechanism underlying mechanical signaling on folliculogenesis was investigated through gene expression profiles, which were compared between and mechanically permissive (soft) and non-permissive (rigid) environments [42]. Gene expression profiles associated with steroidogenic pathways (*Star*, *Cyp11a1*, *Hsd3b1*, *Cyp17a1*, *Cyp19a1* and *Lhcgr*), oxidative stress (*Hif1a*), and water transport (*Aqp7* and *Aqp8)* differed significantly between the two mechanical conditions. The follicle-stimulating hormone (FSH) receptor gene (*Fshr*) was the only gene reported that did not differ significantly between the two conditions at any time point [42]. These results indicate that mechanical environment impacts numerous biochemical pathways that influence follicle growth. In light of this, genomic techniques, such as gene microarrays, may give significant insight into the complex interactions between a follicle and its environment.

## Conclusion

The application of biomaterials to reproductive biology provides a means to advance scientific understanding of reproduction and holds promise for translation to clinical use. Currently, an alginate encapsulation system can be used to obtain a live birth in mice, but further optimization is required to achieve this result in humans. Interaction between a material and a follicle during in vitro culture are complex and result from changes in transport properties, physical support of a 3D architecture, and biological and mechanical signaling. Characterizing follicular interactions with its environment draws from principles in engineering, biology, and medicine; exemplifying the need for an interdisciplinary approach to improve existing methods for in vitro folliculogenesis. By creating systems with tunable properties, scientists and engineers can advance reproductive technologies and provide scientific insight to the field of reproduction.

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# Chapter 3
# Gamete Preservation

**Susan L. Barrett and Teresa K. Woodruff**

## Introduction

With the increase in survivorship following cancer for women in their reproductive years, as well as an increase in survivorship with childhood cancers, there is a demand for perfecting current fertility preservation methods and generating new options for patients who are unable to pursue the conventional course of fertility treatments. Cryopreservation using a slow-cooling method for embryos is currently the standard-of-care for women wishing to preserve their fertility; other options, such as oocyte cryopreservation and embryo vitrification, have become increasingly accepted methods of fertility preservation.

As important as oocyte and embryo cryopreservation methods are for preserving fertility, some patients may be too sick or too young to undergo fertility treatments or have hormone-sensitive cancers that preclude standard approaches; therefore, other preservation options must be explored. Ovarian tissue cryopreservation followed by ovarian tissue transplant and follicle cryopreservation followed by in vitro follicle maturation are experimental techniques that have shown promising results. This chapter will discuss current methods of gamete preservation as well as new, experimental options to preserve immature gametes. An overview of ovarian biology, as well as the science of cryobiology, is discussed to help the reader better understand the circumstances under which different techniques may be used.

## Organization of Gametes in the Human Ovary

The human ovary is divided into three main areas (Fig. 3.1): the hilum, the inner medulla, and the outer cortex. The hilum is the area attached to the mesovarium and it is the entry point for nerves and blood vessels serving the ovary. The medulla is the

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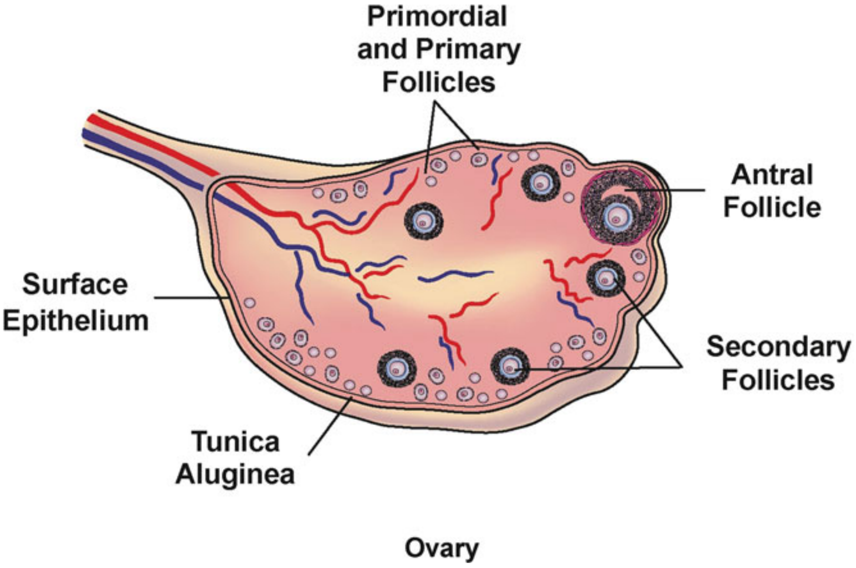

**Fig. 3.1** A human ovary showing the blood supply feeding the arrangement of follicles within the ovarian cortex

central vascular region of the ovary that nourishes immature and growing follicles with necessary hormones and gas exchange. The ovarian cortex, which is approximately 2–3 mm thick and surrounds the central medulla, contains all immature and growing germ cells as well as supportive and endocrine hormone-producing cells. The dense outer layer of the cortex, just under the surface epithelium, is called the tunica albuginea and is filled with dense connective tissue that gives support to the primordial follicle population.

At the time of birth, the human ovary contains the total number of germ cells it will need and use through the reproductive years [1–4]. At this time, all germ cells exist as immature oocytes inside primordial follicles, the smallest functional units of the ovary. Each follicle is comprised of an oocyte surrounded by few interconnected squamous epithelia cells and a basal lamina. In a prepubescent ovary, primordial follicles are scattered throughout the cortex with the majority of the follicles residing near the outer edge of the ovarian cortex [5]. During childhood, low levels of gonadotropins stimulate some of the follicles to exit the arrested primordial state and begin the process of follicle growth; however, these follicles become atretic and do not produce mature oocytes [6, 7]. It is not until the onset of puberty that selected primordial follicles undergo follicle growth, or folliculogenesis, in a cyclic fashion.

In folliculogenesis, the growth of selected follicles proceeds from the primordial to primary follicle stage, during which the squamous epithelium becomes cuboidal in shape and proliferates to form one complete layer of follicle cells. At this time, the central oocyte also begins to grow and secrete proteins on its surface, generating a protective shell called the zona pellucida [8]. The follicle continues to grow with proliferation of follicle or granulosa cells to form multiple cell layers surrounding the oocyte, which in turn stimulate the growth of the oocyte by producing paracrine factors and forming physical cell–cell interactions. As the follicle increases in size, the antral cavity forms, separating the follicle cells into two distinct types of supportive cells, the mural and cumulus granulosa. The mural granulosa remain toward the outer edge of the follicle and express an abundance of luteinizing hormone (LH) receptor, which is essential for ovulation in response to the LH surge. These cells, in conjunction with the theca cells that surround the follicle externally, are essential for aromatization (or conversion) of testosterone to estradiol [9]. The cumulus granulosa cells stay connected to the oocyte and support and nourish the growing oocyte by transporting necessary molecules such as amino acids [10, 11], cAMP [12, 13], glucose [14], and pyruvate [15] through gap junctions. As follicles grow, the fluid-filled antral cavity expands, pushing outward and reaching preovulatory sizes of 12–15 mm in diameter. These mature follicles contain oocytes that are capable of resuming meiosis and undergoing fertilization [4, 16]. For an excellent review on hormone regulation in follicular development, see Zeleznik et al. [17].

## Cryopreservation Techniques

Cryopreservation holds tissues at temperatures between –140 and –200°C, at which no biological activity can occur, producing a state of “suspended animation” of tissues that can be maintained indefinitely [18]. It is the process of cooling and warming, not long-term cryo-storage, that harms cells or tissue [19]. Currently, there are two main approaches for cryopreservation: slow-cooling and vitrification. The success of either of these approaches depends upon the tissue, the cryoprotectant, and the freezing vessel used.

The most important hurdle in cryopreservation is avoiding the phase transition between water and ice inside the cell. Because water is everywhere in a cell and is important for the function of macromolecules and larger structures such as lipid membranes, the formation of large ice crystals upon cooling destroys cellular components and ruptures intact membranes [20]. Interestingly, pure water will supercool substantially and form ice only at approximately –39°C [18], which is much lower than the temperature at which ice is thermodynamically stable (<0°C). Impurities, such as dust, act as ice nucleators, initiating large crystal formation at temperatures well above –39°C [18]. However, allowing ice crystals to form at temperatures more than a few degrees below zero during cooling has been shown to damage embryos and oocytes [21]. To initiate crystal formation in a solution at higher temperatures, the solution must be seeded with ice either by the addition of an ice crystal or by touching it with something colder, such as a forceps dipped in liquid nitrogen, as is done in the laboratory. As ice crystals grow, the volume of the unfrozen solution decreases, thus increasing the concentration of solutes (e.g., salt), which not only helps to reduce ice formation inside the cell but also severely dehydrates cells and can cause cell damage and death [22–24].

Cryoprotectants are defined functionally as any compound that increases cell survivability when used in a cryopreservation method. There are many different types of cryoprotectants, including alcohols, sugars, oils, and starches, and each type acts through different mechanisms. However, a good cryoprotectant is one that can preserve cell structures and is not toxic. James Lovelock first described the mechanism of action of cryoprotectants in his experiments showing that erythrocytes (red blood cells) freeze at lower temperatures when combined with glycerol. He found that the increase in salt concentration resulting from ice crystal formation causes hemolysis [25, 26]. His work highlights the delicate balance between the many factors that must be considered when developing a successful cryopreservation method.

Currently, there are three widely used permeating cryoprotectants in fertility preservation: dimethyl sulfoxide (DMSO), ethylene glycol (EG), and propylene glycol (PG). These cryoprotectants have similar properties: solubility in water at low temperatures, cell permeability, and relatively low toxicity. However, each of these cryoprotectants also has different degrees of membrane permeability, as has been shown with mammalian oocytes [27–29]. Mouse oocytes seem very hearty and are capable of being cryopreserved using several different cryoprotectants; however, evidence suggests that EG is less toxic to mouse oocytes that have resumed meiosis and reached metaphase-II (MII) [30–32]. In contrast, rhesus monkey oocytes are much more sensitive to cryoprotectants and have been shown to be less permeable to glycerol than to PG, EG, and DMSO, and at room temperature, the oocytes are more permeable to PG than to the other cryoprotectants [28, 33]. Interestingly, it was found that PG causes potentially lethal effects when used in human oocyte cryopreservation protocols designed for DMSO. By incubating oocytes in PG at a higher incubation temperature for a shorter time, it may be possible to prevent oocyte lysis [34].

Conventional cryopreservation is the process of slow-rate freezing in which a relatively low concentration of cryoprotectant is used (∼1.5 (M)olar), showing little toxicity to cells or tissue [35]. As cryoprotectant is added to cells, it results in initial cellular dehydration followed by a return to isotonic volume with the permeation of cryoprotectant and water. Generally, cells are cooled slowly using a controlled-rate freezing machine, which allows samples to be cooled at various rates; ovarian tissue is generally cryopreserved at 2°C/min prior to ice seeding and 0.3°C/min after crystallization to ensure the tissue is dehydrated before intracellular ice formation occurs. Optimal rates to minimize intracellular ice formation vary among cell and tissue types; for example, stem cells survive better at a freezing rate of 1°C/min and red blood cells at a rate of 1,000°C/min [35].

As mentioned above, extracellular ice nucleation is triggered manually and must be performed above the temperature of intracellular ice formation. The temperature at which optimal nucleation is performed is determined by the cryoprotectant used as well as the characteristics of the cells [36]. It has been shown that the optimal seeding temperature for human oocytes [36] is different from that for primate [37] and mouse oocytes [38, 39] and varies depending on the meiotic stage of the oocyte [36].

Slow cryopreservation has been used for a number of years; however, in some instances, it can be inconsistent and require expensive equipment. More recently, the process of vitrification has shown to be more successful for some cell and tissue types. Vitrification is a process that uses very high rates of cooling, so fast that water is solidified without crystallization, "like glass." Some investigations of vitrification have shown that extremely high concentrations of cryoprotectants do not crystallize when cooled, even if it is done slowly. This approach is attractive from a technical standpoint; unfortunately, cyroprotectant solutions are toxic to cells at very high concentrations. Solute toxicity is a major drawback of using vitrification for preservation, even with high cooling rates. To reduce toxicity, concentrations of cryoprotectants can be lowered as long as cooling is fast enough to preclude ice formation. For example, the cooling rate for embryos exposed to 8.5 M ethylene glycol must be at least 100,000°C/min for vitrification to occur [40]. To achieve an extremely rapid rate of cooling, a small volume of solution must be used. Recently, specialized storage devices designed to achieve rapid rates of cooling have been designed for the vitrification of eggs and embryos. They hold a very small volume of solution, usually less than 1 μl. These devices have various configurations; the ideal device is covered by a thin wall of plastic and can be submerged directly into liquid nitrogen, thus maximizing the cooling rate. Vitrification is more difficult for sizeable tissue samples that require larger amounts of cryosolution, simply due to the inability to be cooled so quickly.

Although many cells and tissues can be successfully cryopreserved using slow-freeze methods or vitrification methods without intracellular ice formation and can be stored in liquid nitrogen indefinitely, there is still a risk of ice formation during the thawing process if it is conducted improperly. If samples are thawed slowly, ice crystals can form and/or grow causing more damage; however, if samples are thawed rapidly enough, there is little time for ice nucleation and growth to occur [41, 42]. After thawing, there is further risk of damage during the course of removing cryoprotectants. If cells are immediately put into a significantly lower concentration of cryoprotectant, water will rapidly move into the cell and the cells can swell and burst. Therefore, it is usually advised that a series of decreasing concentrations of cryoprotectant is used to slowly remove the cryoprotectants and gently rehydrate cells. As an alternative, it can also be very effective to use a non-penetrating cryoprotectant such as sucrose to reduce osmotic shock during the step-down process [43].

## Embryo and Oocyte Cryopreservation

During the course of the last 55 years, the science of reproductive biology, namely in vitro fertilization (IVF), has coincided with the ability to preserve embryos and oocytes [18]. The storage of gametes is no longer reserved for infertile couples; it now exists as an option for women who wish to preserve their fertility for various reasons. With advances in oncology and anti-cancer therapy, more reproductive-age women are surviving cancer. Unfortunately, many anti-cancer regimens and treatments for other diseases, such as autoimmune disorders, are gonadotoxic [44, 45]. Depending on the diagnosis, some women are able to postpone treatment and proceed through ovarian stimulation in order to collect oocytes from preovulatory follicles for either oocyte cryopreservation or fertilization and subsequent embryo cryopreservation.

During the last 30 years, ovarian stimulation protocols have been perfected, sometimes generating numerous mature oocytes. Prior to the development and use of cryopreservation in the clinic, women were limited in the number of oocytes they were able to fertilize and had to discard excess gametes [46]. Today, a large number of embryos are cryopreserved as standard-of-care in order to avoid unnecessary rounds of hormone stimulation. Cryopreservation of embryos and oocytes are the best options for pursuing a family for women undergoing fertility preservation, with or without a cancer diagnosis [47, 48]. The first successful embryo cryopreservation was performed with eight-cell mouse embryos in 1972 [49, 50], and it took less than a decade after the birth of Louise Brown [51] for the successful cryopreservation and re-implantation of a human eight-cell embryo [52–54]. Since then, protocols have been developed and proved successful for cryopreservation of human embryos of all developmental stages [52, 53]. The survival rate for slow-rate cryopreservation is approximately 75%, with a pregnancy rate between 20 and 30% per transfer [55]. Though vitrification of embryos has been reported to have a 90% survivability rate and a higher pregnancy rate than slow-freeze protocols, it has not yet replaced conventional methods of embryo cryopreservation [56, 57].

Although embryo cryopreservation has been successful, there are situations in which oocytes must be cryopreserved. Cryopreservation of oocytes not only avoids ethical issues surrounding the preservation and long-term storage of embryos but is ideal for women who do not have a male partner or sperm donor at the time of ovarian stimulation. However, cryopreservation of oocytes has been shown to be much more complicated than cryopreservation of embryos. Approximately 50–65% of oocytes survive slow-rate freezing, and they are usually damaged from intracellular ice formation due to their large cytoplasmic volume [58]. The majority of oocytes that are cryopreserved are mature, aspirated from large preovulatory follicles, but they are not fertilized in vitro. They are arrested at MII, at which point the oocyte contains a small spindle of microtubules that aligns the maternal chromosomes. Unfortunately, this spindle is extremely sensitive to changes in temperature, which results in the depolymerization of microtubule fibers. Upon the thawing process, microtubules attempt to repolymerize, resulting in abnormal spindles and misaligned chromosomes [33, 59, 60]. In the last few years, new protocols, including the development of vitrification methodologies, have increased the survivability of cryopreserved oocytes up to 80% [61, 62].

Another source of oocytes for gamete preservation is ovarian tissue removed for ovarian tissue cryopreservation. Large follicles $\geq$1 mm can easily be seen on the ovarian cortex and follicles greater than 5 mm may be aspirated to obtain immature cumulus-oocyte complexes. As the ovarian tissue is processed (discussed below), smaller antral follicles rupture releasing oocytes that fall to the bottom of the dish ranging in size and quality from incompetent denuded oocytes to larger cumulus

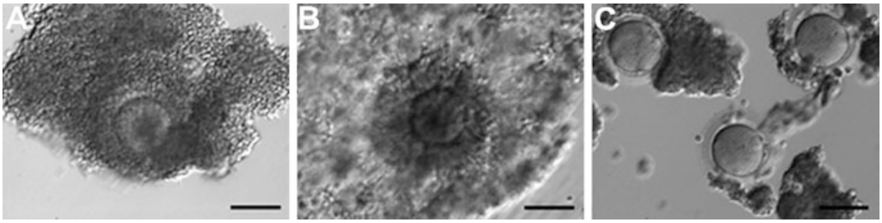

**Fig. 3.2** Human cumulus–oocyte complexes isolated from large antral follicles during the tissue collection process at 0 h (**a**), 24 h (**b**), and 40 h (**c**) during the in vitro maturation process. *Black* measurement bar represents 100 μm

enclosed oocytes (Fig. 3.2a). Oocytes are collected from the bottom of every dish used and matured in vitro for up to 40 h. By 24 h in culture the cumulus granulosa, surrounding the oocyte, begins to mucify resulting in cumulus cell differentiation and expansion (Fig. 3.2b). By 40 h, oocytes are stripped of cumulus cells and are examined for meiotic stage (Fig. 3.2c); the resulting MII oocytes are vitrified for potential future use. Although there have been numerous reported pregnancies with in vivo matured cryopreserved oocytes [63–66], there have been few pregnancies using vitrified in vitro matured oocytes and no pregnancies have been reported with in vitro matured oocytes preserved by slow-rate cryopreservation [63, 64, 67].

## Experimental Options for Gamete Preservation

During the last few years, there has been great progress in the field of oncofertility. Much research has been done in this field with the hope of broadening the range of fertility preservation options and for women facing potentially gonadotoxic treatments.

### *Ovarian Tissue Cryopreservation and Transplantation*

Not all women are able to delay anti-cancer regimens for the 2–5 weeks needed to undergo hormonal stimulation to preserve mature oocytes or embryos. Other options have been developed to preserve gametes in order to restore fertility in women after treatment. Ovarian tissue cryopreservation and subsequent tissue transplant is still an experimental procedure that involves the removal of an ovary or piece of cortical tissue (Fig. 3.3a), which is cut into small pieces (Fig. 3.3b) that are cryopreserved until a woman chooses to restore her fertility. It is currently the only methodology that is feasible for fertility preservation in young girls [67, 68]. As mentioned previously, the cortex of a normal ovary is filled with arrested, immature, primordial follicles; there may be hundreds of primordial follicles in a 1-mm$^3$ piece of tissue [69]. Analysis of human ovarian cortical tissue has shown that the number of primordial follicles varies in the ovarian cortex and is directly correlated with

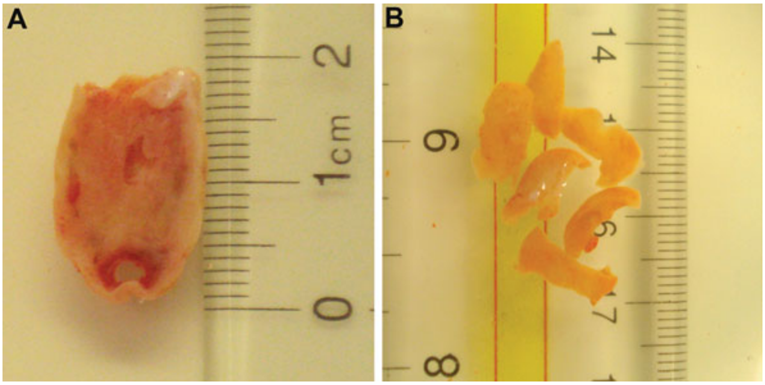

**Fig. 3.3** Bisected human ovary showing the thick outer cortex and the inner vascular medulla (**a**). Human ovarian cortex cut into strips prior to cryopreservation (**b**)

a woman's age [70]. Unlike freezing embryos and mature oocytes, which contain large cytoplasmic volumes, the primordial follicles in cortical tissue contain small oocytes that easily survive the freezing process when the tissue is cut into small strips of 1–2 mm × 1–2 mm × 10 mm (Fig. 3.3b).

Ovarian tissue transplant following tissue cryopreservation was first successfully completed in mouse [71, 72] and has since been successful in sheep [73] and primates, whose ovaries more resemble those of humans [74]. In the last few years, more than 30 cases have described the transplantation of cryopreserved or vitrified tissue to heterotopic sites such as the forearm [75], as well orthotopic sites such as the abdomen [76] or back to the residual ovary [77, 78]. It was found, on average, that hormone cyclicity resumed within 3 and 5 months of the ovarian tissue transplant, which represents the time it takes for follicle recruitment and subsequent growth [77, 79, 80]. Ovarian tissue transplantation has resulted in the birth of six children to date [77, 78, 81]. Although several groups have reported high levels of follicle-stimulating hormone (FSH) after transplant, which is associated with a low follicular reserve [79, 82], it is still too early to tell how long these transplants will remain functional. It is hypothesized that a single transplant could last several years depending on the age at which the tissue was removed as well as tissue exposure to gonadotoxic treatment prior to removal [83, 84]. For an excellent, in-depth review of ovarian tissue transplant see Demeestere et al. [85].

## *In Vitro Follicle Cryopreservation and Maturation*

There are situations in which women diagnosed with hematologic or ovarian diseases or who have been diagnosed with BRCA1/2 positivity are unable to transplant their stored ovarian cortical tissue due to the possibility that the tissue may contain microscopic lesions [86, 87]. In addition, options for fertility preservation are only available for mature oocytes, embryos, and tissue containing primordial follicles, completely ignoring the vast number of growing yet immature gametes contained within the ovary in primary and early secondary follicles. Experimental studies of individual follicle cryopreservation and subsequent in vitro follicle maturation tackle this last remaining population of female gametes for use in fertility preservation.

As cortical tissue is isolated from the ovary, it can be cut into thin strips and cryopreserved as mentioned above; however, due to their increased oocyte size, primary and secondary follicles fail to survive the in situ freezing process [19, 88]. It is hypothesized that individual follicle isolation allows for better penetration of cryoprotectants, thus helping to stabilize physical connections between the follicle cells and the oocyte [89]. Therefore, a portion of cortical tissue can be cut into smaller pieces (2 mm$^3$) and treated with enzymes such as liberase or collagenase that will break down stromal tissue to aid in the release of small follicles (Fig. 3.4) [90–92], which then can be cryopreserved for later use. Successful slow-rate cryopreservation of small secondary follicles has been shown in mice [89, 93], as well as in non-human primates and humans [89].

After thawing, individual follicles can be encapsulated into a 3D matrix such as alginate, a hydrogel made from seaweed, which supports free passage of amino acids and secreted hormones and also serves as a scaffold for follicular development [94]. It has been shown that fresh isolated follicles from prepubescent mice are capable of follicle growth from 150 to 350 μm within 8 days of culture in alginate [95]. These follicles secrete estradiol and progesterone at elevated levels upon antrum formation, which correlates with an increase in *Star* and *Cyp19a1* gene expression necessary for steroid production and is characteristic of healthy follicles [96]. Within 8–10 days of follicle growth in the 3D matrix, follicles can be stimulated with FSH and LH to resume meiotic maturation and cumulus expansion, and the oocyte can then be fertilized, giving rise to healthy offspring [92]. Thus far, cryopreserved mouse follicles are capable of full follicle development in

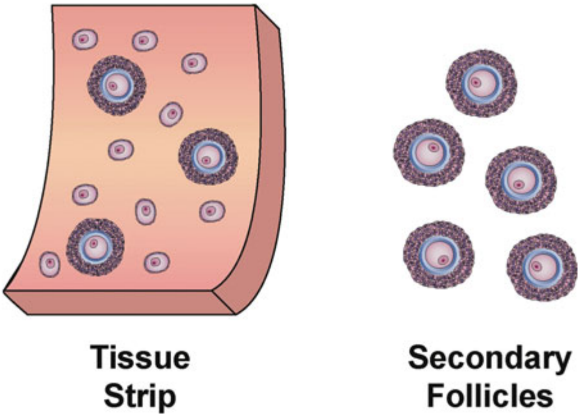

**Fig. 3.4** The ovary is dissected into tissue pieces that are either cryopreserved or treated with collagenase for the dissection of secondary follicles used for in vitro follicle growth

the 3D alginate matrix, producing healthy oocytes that can be fertilized and support embryonic development up to the blastocyst stage [89].

Recently, mouse protocols have been adapted for long-term culture of non-human primate and human follicles. It is thought that since a primate follicle takes much longer than a mouse follicle to grow from primordial follicle to a preovulatory follicle (>90 days), the same would be true in in vitro culture [97]. Thus far, 30-day cultures have succeeded for both rhesus macaque [98] and human [99] secondary follicles encapsulated in alginate hydrogel. Primate follicles isolated from either the follicular phase or the luteal phase of the menstrual cycle were able to grow during a 14-day culture period; however, follicular phase follicle survival (78%) was much higher than that of luteal phase follicles (42%), which could be attributed to the larger size of follicles isolated in the follicular phase [98]. Encapsulated human secondary follicles isolated from ovarian tissue donated from cancer patients have also been successfully cultured for up to 30 days, with follicles forming large antral cavities and reaching sizes greater than 1 mm [99]. Follicle peptide and steroid hormone production appears to mimic that of antral follicles in vivo, with a characteristic increase in inhibin A and anti-Müllerian hormone (AMH) during follicle growth. Follicles that continued to grow showed a decrease in inhibin B, which correlates with dominant, preovulatory follicle selection. Thus far, 30-day human follicle cultures are capable of supporting the growth of full-sized oocytes that are competent for fertilization (i.e., MII stage) [99].

Primate and human secondary follicle growth in culture has also been tested following individual follicle cryopreservation [89]. Although primate and human secondary follicles are able to survive the cryopreservation process and grow from an average 175–250 μm (primate) and 125–200 μm (human) during a 6-day culture period, the length of the culture period must be extended in order to see the full effects of cryopreservation on oocyte development [89]. Isolation and cryopreservation of individual secondary follicles expands option for women and children who cannot immediately seek fertility treatments and are not good candidates for other fertility sparing options such as ovarian tissue cryopreservation.

## Conclusion

There have been great advances in gamete preservation both for infertile couples and for women and young girls who are faced with life-threatening diseases. Perfecting oocyte and embryo cryopreservation as well as developing new procedures, such as ovarian tissue cryopreservation/transplant and follicle cryopreservation followed by in vitro follicle maturation, is expected to generate more options for fertility preservation.

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# Chapter 4
# To Transplant or Not to Transplant – That Is the Question

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## Introduction

Successful fresh human ovary transplantation was first reported between monozygotic twins discordant for premature ovarian failure (POF) using a cortical grafting technique [1, 2]. Normal menstrual cycles resumed after 4 months, and spontaneous pregnancy leading to a healthy child occurred 1 month later. Subsequently, a series of seven more consecutive successful cases was reported, for a total of eight, all demonstrating normal ovulatory menstruation [3, 4]. A ninth successful case using a different technique, microvascular intact whole ovary transplantation, was reported recently, again with return of normal ovulatory cycles, spontaneous pregnancy, and delivery of a healthy child [5]. This unusual series of ovary transplants between monozygotic twin sisters afforded a remarkable opportunity to study the effect of transplant ischemia and cryopreservation on the success of fresh and frozen ovarian grafts without the concern of immunosuppression. We can apply the techniques of cryopreservation and transplantation gleaned from these transplants to preserve fertility in patients who are about to undergo otherwise sterilizing cancer treatment.

The indication in all of these cases was complete ovarian failure (POF) in one sister who wished to have children, whereas the other sister was fertile and already had her family complete. In each case, careful consideration was given to other treatment options such as donor egg IVF and adoption. Thus far, 12 pregnancies and 8 healthy babies have resulted from these nine homozygotic transplants. In seven of these nine fresh ovary transplants between monozygotic non-rejecting sisters, some ovarian cortical tissue was frozen for a future grafting, in case the transplanted ovary would run out of eggs and cease to function [6]. Our results in these monozygotic twins with discordant ovarian failure, using both fresh and frozen ovarian grafts, form the basis of our technical improvements in ovary freezing and transplants for young cancer patients. “These strategies are reviewed with their technical and utilization limitations; and a discussion will be provided of the next steps that will

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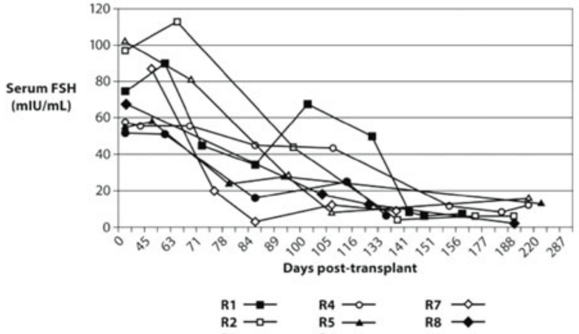
proceed eventually to the first attempt at fertilization of an oocyte from an in vitro matured human follicle with embryo transfer, which can be applied in cases where ovarian tissue transplantation is not recommended."

## Transplant Technologies and Their Success

First we needed to distinguish between the effect of ischemia time versus that of cryopreservation, and how to reduce oocyte loss from both. We have eliminated ischemic damage with intact whole ovary microsurgical transplantation, but this technique is much more difficult than cortical grafting and is complex and risky [5]. So cortical grafting is best for popular acceptance. However, the simpler cortical graft technique in the past had been problematic, with only sporadic reported success. For example, a dramatic loss of oocytes had been noted in some studies of ovarian cortical grafting in animals [7]. But in other animal studies apparently normal lifetime graft survival has been observed [8]. In one human study, there was a maximum graft survival lifetime of only 2 years, but the clinical situation was very convoluted, i.e., older women undergoing hysterectomy and oophorectomy [9]. In the cases of autotransplantation of thawed ovarian tissue in cancer patients, successful results have been few and very sporadic at best [6, 10–12]. It has not been clear whether these problematic outcomes are due to cryopreservation damage, or to the ischemia time after cortical grafting until revascularization occurs, or in some cases simply to prior damage from chemotherapy [13].

We have eliminated these concerns in our series of monozygotic sisters and also in frozen autografts. In 12 of these procedures, 9 fresh and 3 frozen, we have demonstrated the surgical robustness of the procedure when there are no immunological concerns, and with improved methods of cryopreservation [14]. In this study, we have observed in humans that fresh cortical ovarian grafts result in very little oocyte loss and yield normal duration of function (when using microsurgical techniques). Furthermore, we have found that although slow-freezing results in over a 60% loss of oocyte viability, vitrification may mitigate this cryo-induced oocyte loss, and there should therefore be no obvious difference in results between fresh or frozen cortical grafts (Fig. 4.1). Finally, only one out of the nine cases failed to conceive spontaneously (a 40-year-old woman), and all patients but one have one or more live babies resulting from this procedure.

It is estimated that two normal ovaries in a 25-year-old with normal ovarian reserve should yield approximately 26 years of function [15]. Therefore, one-fourth of one ovary might be expected to represent one-eighth of normal ovarian reserve in a typical 25-year-old. Thus, 3–4 years of graft function would be compatible with minimal loss of oocytes. We used the duration of fresh graft function as a baseline, and then compared oocyte viability in a strip of fresh graft to frozen thawed grafts cryopreserved by slow freeze versus vitrification. Thus, we estimated the overall duration of function of cortical grafts and evaluated the oocyte loss to be minimal.



No Difference Between Fresh and Frozen

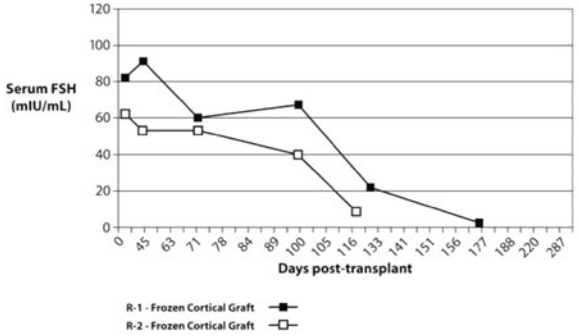


**Fig. 4.1** There is no difference in the rate of return of serum FSH to normal between fresh and frozen ovarian grafts

## Surgical Technique

Under general anesthesia, one ovary was removed intact by laparoscopy or by mini-laparotomy and the cortex was transplanted onto the decorticated medulla of the recipient (Fig. 4.2). The donor ovary is transferred to a Petri dish with Leibowitz (L-15) medium that is placed upon cold saline ice slush. It is then dissected ex-vivo into thin strips of cortex. The following surgical principles were applied in all cases: (a) thin the cortical tissue down to a bare 0.75–1.0 mm to promote more rapid revascularization, (b) obtain perfect hemostasis of graft bed with micro-bipolar forceps, (c) suture securely with 9-0 nylon interrupted sutures to prevent micro-hematoma formation under the graft, (d) use the ovarian medulla to obtain the richest angiogenic factors and the most rapid graft revascularization, and (e) continual pulsatile irrigation with heparinized saline to prevent adhesion formation [2, 4, 5].

The normal predicted survival of ovarian grafts in our series of patients demonstrates that there is probably not a huge oocyte loss from the transplant itself, similar to our autotransplantation studies in cattle [14]. The reason for our high success with fresh cortical grafts could be related to a surgical technique that avoids micro-hematoma formation under the graft, and uses a very thin 0.75-mm slice of cortex.

**Fig. 4.2** Completed ovarian cortical graft through minilap incision

Plastic surgeons use pressure dressings over skin grafts to avoid this most common cause of graft ischemia and delayed vascularization. Since we have no such option intra-abdominally, we use multiple minuscule stitches of 9-0 or 10-0 nylon sutures, and prepare the graft bed carefully with pinpoint microbipolar hemostasis while at the same time employing constant irrigation with heparinized saline to avoid adhesion formation. Finally, it is probable that an orthotopic location allows for better ovarian function than a heterotopic one, perhaps due to more normal tissue pressure during ovarian follicle maturation [16, 17–19].

The question comes up whether cortical tissue grafts are as favorable as a microvascular whole ovary transplant as suggested by Bedaiway and Falcone [20, 21]. Thinking that this might avoid the ischemia time associated with waiting several days for the medullary graft bed to revascularize the transplanted cortex, we performed a successful case of microvascular whole intact ovary transplant in a woman who was more interested in long-term function than pregnancy [5]. She began to spontaneously cycle and ovulate, and conceived a healthy baby girl. Unfortunately, this is a difficult and major operation that requires very extensive micro-vascular surgical expertise, and cryopreservation of an intact whole ovary is more problematic than vitrification of a cortical tissue slice.

## Ovarian Tissue Vitrification

For vitrification, the ovary cortex was cut into pieces 1 × 10 × 10 mm. The precise 1-mm tissue thickness was guaranteed with a tissue slicer designed explicitly for this purpose. The tissue slicer plate has a 1 × 10 × 10 mm cubic space. The ovary is cut between the slicer and the surface of ovary using a sharp edge. The ultra-thinness of the tissue is thought to be crucial, not only for the cryopreservation but also for the rapidity of revascularization after grafting. Ovarian tissues are initially equilibrated in 7.5% ethylene glycol (EG) and 7.5% dimethyl sulfoxide (DMSO) in handling medium [HM; HEPES-buffered TCM-199 solution supplemented with 20% (v/v) synthetic serum substitute (SSS; Irvine Scientific, Santa Ana, CA, USA)] for 25 min followed by a second equilibration in 20% EG and 20% DMSO with 0.5 mol/l sucrose for 15 min, or until the tissue sinks to the bottom of the test tube indicating complete absorption. Ovarian tissues are then placed in a minimum volume of solution onto a thin metal strip (Cryotissue; Kitazato BioPharma, Fujinomiya, Japan), and submerged directly into sterile liquid nitrogen, following which the strip was inserted into a protective container and placed into a liquid nitrogen storage tank. For warming, the Cryotissue metal strip is immersed directly into 40 ml of 37°C HM solution supplemented with 1.0 mol/1 sucrose for 1 min. Then, ovary tissues are transferred into 15 ml of 0.5 mol/1 sucrose HM solution for 5 min at room temperature and washed twice in HM solution for 10 min before either viability analysis or transplantation.

Fresh ovarian tissues (examining 358 oocytes) were not significantly different in oocyte viability from vitrified tissues (examining 1,122 oocytes) for a 91.9% and an 89.1% viability rate, respectively. Slow-freeze ovarian tissue by contrast (examining 821 oocytes) demonstrated an oocyte viability rate of only 41.7%. Vitrification resulted in minimal if any oocyte loss, similar to previous findings in cattle [14]. Thus, freezing by vitrification is not likely to seriously harm the results with ovarian cortical grafting.

## Preserving Fertility in Cancer Patients

The major reason for the current intense interest in ovary freezing and transplantation is that at least one in 250 women of reproductive age [22] are cancer survivors. Today, 90% of these young women will be cured of their cancer [23, 24]. Yet the very treatment which will cure them usually compromises their fertility by destroying all or a large part of their ovarian follicle reserve [10, 25–27]. Most such young women with cancer are highly interested in trying to preserve their fertility so they might have children in the future [28, 29]. However, their treatment is likely to reduce their fertility or render them completely sterile. Also, for children, pediatric patients may not understand the full implications of cancer treatment for future parenthood, but fertility preservation is equally important for them, and they do not have the option of using IVF technology for oocyte or embryo banking.

A secondary reason for the current interest in fertility preservation is an increasing delay in age in developed countries for women to try to conceive [30–33]. Yet fertility naturally declines with age in all women, even those who have no other health problems. This reduced fertility in women from their teen years to their early 1940s is caused by a decreasing number and decreasing quality of their eggs [34–37]. Thus, we are experiencing a worldwide epidemic increase in infertility caused simply by ovarian aging.

The uterus does not seem to play a significant role in this age-related decline in fertility as evidenced by the high pregnancy rate in older women using eggs donated from younger women [36]. Therefore, it has been widely hoped that ovarian cryopreservation and subsequent transplantation of thawed tissue years later, after the patient has been cured of cancer or wishes to have children, could be an effective resolution to this dilemma [1]. In fact, thus far in humans there have been 13 healthy babies born from fresh or frozen ovarian grafting (Table 4.1).

**Table 4.1** Delivered pregnancies after transplanting fresh and cryopreserved ovarian tissue (13 babies). The worldwide experience with ovary transplantation, both frozen and fresh, is obviously quite robust

| Patient type | Transplant | Country | References |
|---|---|---|---|
| Premature ovarian failure | Fresh MZ twin orthotopic cortical strip | USA | Silber et al. (2005) 7 babies |
| Hodgkin's lymphoma | Frozen autograft orthotopic cortical strip | Belgium | Donnez et al. [16] |
| Non-Hodgkin's lymphoma | Frozen autograft orthotopic cortical strip | Israel | Meirow et al. [34] |
| Ewing's sarcoma | Frozen autograft orthotopic cortical strip | Denmark | Andersen et al. (2008) |
| Hodgkin's lymphoma | Frozen autograft orthotopic cortical strip | Belgium | Demeestere et al. [13] |
| Premature ovarian failure | Frozen MZ twin orthotopic cortical strip | USA | Silber et al. [38] 1 baby |

Although thousands of ovarian tissue samples have been banked in clinics worldwide, clinical success rates cannot be defined yet because very few women have had a transplant after cancer treatment, and none for ovarian ageing. While the MZ twin series involved histocompatible donor tissue instead of an autograft, and healthy individuals rather than cancer patients, this is the largest series of ovarian transplants to date and provides rare information for guiding fertility preservation practices and counseling patients about the likelihood of success.

As mentioned in the *Introduction* section, transplantation ischemia has sometimes been considered to be a more limiting factor for the functional lifespan of grafts than cryopreservation per se. This conclusion was however drawn from experiments in which bovine tissue was xenografted to SCID-mice, using the kidney capsule instead of the orthotopic site [7]. It would be unreasonable to expect such a transplant not to suffer severe oocyte loss irrespective of any additional cryoinjury. Since a balanced experimental design is not feasible in human patients for ethical reasons, it is difficult to draw inferences about the impact of ischemia except for radically different surgical strategies. Ischemia time is reduced from an estimated 2–4 days with cortical tissue slices to only 1–2 h for restoring perfusion after microvascular surgery. Studies in rats found no significant loss of follicles in microvascular ovarian transplants [39], but the technique has only been reported for a single successful human case and, although she has delivered a healthy child and is still cycling with low serum FSH, it is far too early to confirm the degree of advantage in long-term function [5].

Although no firm verdict can yet be drawn, data from the MZ twin series provide striking proof of the effectiveness of fresh cortical transplants and also some reassurance about their reproductive safety. Eight healthy babies have been born to six women. Assisted reproductive technology was not required, natural conception mostly occurring within the first year post-surgery and one instance after the first ovulation. Early conception is not a rule, however, because one woman conceived after 3 years and another had her second child over 4 years after her transplant. It is not surprising that at 40 years old the oldest recipient (#5) has not become pregnant so far, even with the entire cortex of the donor ovary. Ovarian transplants involve a single operation with a relatively low surgical burden and low cost, and the major advantages of no further medicalization of reproduction by IVF, and singleton pregnancies. There have been few miscarriages to date, nor have there been any birth defects or obstetric complications associated with transplantation.

We surmise that careful preparation of the donor tissue as a very thin wafer, avoiding micro-hematoma formation between the highly vascular graft bed, and closely apposing the graft to the medulla, all contributed to the success of this series by prompting rapid revascularization. The orthotopic location may also be important, not only for natural conception but also for avoiding pressure from neighboring tissues, which in some heterotopic sites can distort growing follicles and affect the physiology.

No amount of surgical skill can compensate for poor cryopreservation. The evidence of viability markers indicated that <50% of human oocytes survived the slow-freezing protocol using in 1,2-propanediol, which has been the standard method for ovarian tissue since the pioneering studies in sheep [1, 40–42]. Moreover, ultrastructural studies, which reveal much more detail of cellular injury than histology, have shown major damage from slow-freezing in the stromal tissue which is needed to support follicle growth and provide precursor cells for the theca. Our studies with bovine ovaries have revealed that vitrification can produce results superior to standard cryopreservation [14], a conclusion that was confirmed in the present study although it is too early to report the results of human ovarian tissue transplanted after vitrification. Since most centers including our own have mainly used the slow-freezing cryopreservation protocol, it is reassuring that two viable pregnancies were obtained in our study as well as five others for cancer patients in other centres [6, 11, 12, 43–44]. The percentage of viable oocytes in vitrified tissue was remarkably similar to that of fresh tissue controls, suggesting that vitrification might provide even better results after transplantation than slow freeze cryopreservation.

Finally, what is the future for women whose ovaries were frozen before undergoing treatment of leukemia or breast cancers that might have already metastasized to the ovary [22, 45–54]. Hodgkin's disease is the safest cancer for transplanting ovarian tissue back to the patient [16–19, 55]. The tumors least likely to present with ovarian metastasis are Hodgkins and osteogenic sarcoma. But what can be done with frozen ovarian tissue of the leukemia survivor if there happen to have been leukemic cells in that tissue? Non-Hodgkins lymphomas, colon, melanoma, pancreas, gastric, and breast cancer, often called Krukenberg tumor, can all metastisize to the ovary

[56–60]. Culturing ovarian tissue to obtain mature follicles for IVF in these patients is currently the subject of intense research efforts. The mysterious clockwork of a precise number of follicles leaving the resting pool daily and maturing over the next 3 months has defied efforts at in vitro maturation of eggs, which is what is necessary to safely use this tissue for helping leukemia patients conceive. But progress is now being made with three-dimensional culturing because one mechanism controlling follicle maturation in the ovarian cortex may be physical pressure and tissue rigidity Using this concept, remarkable progress has been made in culturing ovarian tissue and maturing follicles in vitro [18]. It could even explain why orthotopic transplantation is so robust and heterotopic results have been so disappointing.

## Recent Progress on Culturing Follicles In Vitro

Cryopreserved ovarian tissue can be used for autotransplantation [1, 3–5, 37, 61–62] or in vitro maturation of follicles to produce mature oocytes [45]. The latter approach eliminates the possibility of reintroduction of cancer cells and provides a way to harvest a greater number of mature oocytes. However, in vitro maturation of ovarian follicles has been fraught with many technical challenges [63–66].

The ovarian follicle is a unique structure that contains the egg surrounded by and intimately connected to support cells. In vivo and in vitro studies have established the importance of cell–cell communication in the growth and differentiation of the follicle [67]. In traditional 2-D culture systems, somatic cells detach from the oocyte and spread onto the culture surface, thereby disrupting somatic cell–oocyte communication. The inefficiency of oocyte maturation in the 2-D system has been the primary stumbling block to in vitro maturation protocols. In contrast, 3-D culture systems maintain the overall architecture of the follicle and therefore support the vital communication pathways between the egg and the somatic cells, thereby more effectively allowing normal follicle development [19, 38, 55, 63, 68–70].

In our 3-D culture system, ovarian follicles are encapsulated within hydrogel beads formed from alginate [68, 70]. Alginate is a linear polysaccharide derived from algae and is composed of repeating units of ß-D-mannuronic acid and α-L-guluronic acid [71]. Gelation of alginate by ionic crosslinking of the guluronic residues with calcium is mild, which maintains cell viability. Additionally, alginate has minimal nonspecific protein absorption and cell adhesion and thus serves primarily as a mechanical support to the follicle [72]. Immature follicles can be placed in alginate droplets, which, after gelation, replace the ovarian stroma/matrix and support the 3-D culture of ovarian follicles in vitro. Alginate was chosen for encapsulation since immature mouse follicles can be encapsulated easily in alginate hydrogel beads [68, 70]. Follicles can be removed from alginate by degrading the gel with an alginate-specific enzyme, which has no known interactions with mammalian cells. In addition to mechanical support, alginate is highly porous, thereby allowing soluble factors and hormones to diffuse through the gel between the media and the follicle.

Following encapsulation, follicle growth and oocyte maturation during an 8- to 12-day culture period phenocopied follicle development in vivo, in which follicles form a central fluid-filled antral cavity and the oocyte is surrounded by cumulus cells [68]. Follicles retrieved from the hydrogel were treated with hCG, and approximately 70% of fully-grown oocytes matured to metaphase II after 16 h. These eggs were fertilized in vitro ($\sim$68%, $n = 99$) at rates similar to that achieved with in vivo ovulated mature eggs ($\sim$82%, $n = 65$), indicating that the 3-D hydrogel supports normal oocyte development in a manner far superior to any other method developed to date [19]. Transplantation of embryos derived from follicles cultured in the alginate system into CD1 foster mothers resulted in live births of healthy, fertile offspring from 20% of the transferred embryos, a significant improvement relative to previously reported live birth rates, which are less than 5%.

In vitro and in vivo tissue engineering approaches for previously intractable biological problems have gained significant momentum in the past two decades. Application of tissue-engineering principles to reproductive health and fertility preservation has been promising that the biological obstacles to in vitro follicle development can be overcome. The success of studies in mice using the hydrogel system present a new opportunity to move this technology from the bench to the bedside and to provide fertility options to patients who have only immature follicles available as starting material.

Monkey ovary cortical strips have been transplanted in a variety of sites in vivo with re-initiation of antral follicle growth, oocyte maturation, and, following ICSI and embryo transfer, one live birth [73]. Ongoing studies are assessing factors that impact graft survival and the retention of follicular reserves that will sustain follicle growth and production of healthy, mature oocytes. In 2004, the first human baby was born after orthotopic transplantation of frozen-thawed ovarian tissue in a woman with Hodgkin's lymphoma [6]. Since then there have been several case reports demonstrating that autotransplantation of frozen-thawed ovarian cortical strips can yield human oocytes capable of fertilization and early development [74], pregnancy, and offspring [12, 44]. Thus, the cryopreservation and storage of human ovarian cortex from patients at risk for gametotoxicity during clinical treatments is becoming prevalent and guidelines are being established [75]. Nevertheless, slow-freezing techniques, as well as some transplant techniques, can result in a significant loss of follicles [7, 40, 41] and carry a significant risk of reintroducing cancer cells into the "cured" patient [54, 76]. Newer freezing and surgical techniques discussed in the first part of this chapter have solved the problem of oocyte loss. Nevertheless, autotransplantation of ovarian tissue, especially in young girls, does raise concerns about long-term patient safety [77].

In vitro follicle maturation provides an alternative to autotransplantation by eliminating the risk of reintroducing cancer cells. However, the difficulty of maturing isolated oocytes without their supporting follicle and the failure of small follicles to develop in a 2-D environment have hindered development of in vitro follicle maturation strategies. The limitations of 2-D culture systems may be even greater in primates, which have larger follicles with a longer growth phase [78]. Primate [79] and human [80] primordial follicles maintained in situ in organ culture (1-mm slices) will begin to grow and can reach the secondary stage, but a large percentage of follicles are lost. While ovarian slices retain the general architecture of the follicle, the poor diffusion properties and rigid structure of the tissue likely limit follicle growth and development.

The 3-D alginate hydrogel culture system may offer new opportunities for investigating follicle growth and maturation in primates, and, ultimately, for restoring fertility in female patients following ovarian tissue cryopreservation. In contrast to mice [19], there are no reports to date of human follicles achieving the large to preovulatory stages in vitro [81]. Current research efforts are aimed at evaluating the growth potential of rhesus monkey preantral and antral follicles encapsulated in the alginate hydrogel matrix. Preliminary experiments have demonstrated that early stage and preantral follicles can be grown in vitro to the small and medium antral stage in 24 and 31 days, respectively. This interval is similar to that reported for human follicle culture [81], although success rates appear to be higher. Whether this is due to the use of alginate encapsulation or starting with preantral rather than primordial follicles remains to be determined. Preantral follicles growing to the small antral stage became steroidogenically active, with androgen and estrogen levels rising from low concentrations during the first week of culture to appreciable levels by the end of the second week.

It appears that longer intervals of culture will be required in primates relative to mice to obtain mature preovulatory follicles, and that follicle survival could be dependent upon the phase of the menstrual cycle when ovaries are collected. Nonetheless, initial results provide the first evidence for long-term culture of preantral primate follicles to the antral stage. Future studies will continue to optimize the alginate hydrogel culture system in terms of gel matrix composition and media components, with the goal of producing mature oocytes that are competent for fertilization, culminating in transplantation of embryos and the birth of live, healthy, fertile offspring. Coupled with advances in ovarian tissue cryopreservation, in vitro maturation may provide another option for young cancer patients and women who want to preserve fertility without the potential risks associated with autotransplantation.

## Conclusions and Final Thoughts

A carefully guarded clinical decision is necessary before transplanting ovarian tissue back to cancer patients. Nonetheless, for patients in whom there is no significant risk of ovarian metastasis, ovary tissue transplant may be quite favorable. These results bode well for applications in oncology, as transplantation of ovarian tissue banked at low temperatures is looking more and more promising as an option for preserving fertility. However, in cases where such transplantation would risk the transmission of cancer cells, there may nonetheless be a good option in the future via ovarian follicle culture and IVF.

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# Chapter 5
# Clinical Cases in Oncofertility

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## Introduction

As an emerging interdisciplinary field, oncofertility bridges oncology and reproductive endocrinology and infertility with the goal of expanding reproductive options for women with cancer. In this chapter, we present a series of clinical scenarios encountered in medical practice to illustrate some of the complex issues that arise in this field and offer suggestions for patient care. An increased awareness of the difficult issues involved in oncofertility practice should help prepare clinicians for some of the challenges posed by this rapidly expanding discipline. While the four cases presented here are based on true situations, they have been modified to protect the identity of the patients involved.

### Clinical Scenario 1

Jennifer is a 24-year-old single female with a history of Hodgkin's lymphoma who was found to have recurrent lymphoma 6 months after chemotherapy (ABVD). Her oncologist recommended bone marrow transplant, a treatment that would almost certainly result in permanent infertility. After a thorough discussion of various fertility preservation options, she decided to bank oocytes. She had a history of regular menstrual cycles and was on day 18 of her cycle. Cetrorelix (Cetrotide®) 3 mg was administered subcutaneously and she began menstruating 2 days later. Baseline ultrasound revealed an antral follicle count of 3, serum FSH 9.2 mIU/ml, and estradiol 45 pg/ml. Controlled ovarian stimulation was initiated with recombinant FSH at 450 IU per day. Cetrorelix 0.25 mg was started on day 5. On day 10 of stimulation, estradiol

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was 4,800 and she had 24 growing follicles, the largest measuring 20 mm in mean diameter. Leuprolide acetate was used to trigger final oocyte maturation, she underwent egg retrieval and 15 mature oocytes were vitrified.

## Use of GnRH Antagonist for Luteolysis and Cycle Synchronization

In assisted reproduction, gonadotropin-releasing hormone (GnRH) antagonists have traditionally been utilized during ovarian stimulation to prevent a premature LH surge. Recently, the use of GnRH antagonists during the preceding luteal phase has been explored as a technique to improve ovarian stimulation by inducing corpus luteum breakdown and synchronizing the development of the next wave of follicles. While originally intended for poor IVF responders, GnRH antagonists play an important role in the stimulation of cancer patients for embryo and oocyte cryopreservation by shortening the luteal phase and expediting stimulation and fertility preservation techniques prior to cancer therapy. Taking advantage of its effect on rapid absorption of the corpus luteum, cetrorelix 3 mg is given during the late luteal phase and menses begin a few days later. Patients can then proceed with ovarian stimulation with gonadotropins, and GnRH antagonists are administered when the lead follicle is > 14 mm [1]. The case of Jennifer serves as an example of how luteal GnRH antagonists can be used to shorten the time to stimulation. We have found this protocol to be very useful in cancer patients who have limited time for embryo or oocyte banking prior to life saving cancer therapy.

## GnRH Agonist Trigger to Prevent OHSS

Ovarian hyperstimulation syndrome (OHSS) is one of the most serious complications associated with ovulation induction routinely performed as part of fertility preserving techniques such as oocyte and embryo banking. This syndrome may be associated with ovarian enlargement, intravascular depletion, ascites, liver dysfunction, pulmonary edema, electrolyte imbalance, thromboembolic events, and hemoconcentration [2]. While this syndrome is often self-limited with spontaneous resolution within a few days, severe disease may require hospitalization and intensive care [3]. Although the reported prevalence of severe OHSS is low, ranging from 0.5 to 5%, Jennifer's response to stimulation was surprisingly brisk even though her baseline measures of ovarian reserve appeared to be impaired. Selecting the appropriate ovarian stimulation regimen can be challenging in oncofertility because it is important to balance the risk of OHSS and at the same time procure sufficient oocytes or embryos to maximize the chance of a successful pregnancy in the future. The impact of OHSS can be profound in a cancer patient since this syndrome has the potential to delay and complicate planned lifesaving cancer therapy [4, 5].

As an alternative to traditional human chorionic gonadotropin (hCG) administration to simulate the natural midcycle luteinizing hormone (LH) surge, studies have reported that GnRH agonist (GnRHa) administration successfully induces final oocyte maturation and dramatically reduces the risk of OHSS [5–9]. Indeed, it appears that the risk of OHSS is essentially eliminated because GnRHa's induce an endogenous LH surge with a short half-life and reduced luteal phase steroid concentrations [5, 6]. This technique is particularly convenient in cancer patients pursuing oocyte or embryo banking because luteal support is not needed to sustain a pregnancy. While it is helpful to identify patients at high risk of developing hyperstimulation so that appropriate strategies can be implemented, response to gonadotropins and development of OHSS can be unpredictable. Therefore, we have found the use of the GnRHa to trigger the final maturation of the oocytes particularly valuable for many young cancer patients who are at risk for OHSS and the resulting complications. In the case presented, Jennifer was an ideal candidate for trigger with GnRHa because she over-responded to ovarian stimulation. Indeed, despite her high level of estradiol, she did not develop any signs or symptoms of OHSS.

## Oocyte Cryopreservation

This case also highlights the important and emerging role of oocyte cryopreservation in oncofertility. Although the first human pregnancy resulting from human cryopreserved oocytes was reported in 1986 [10], oocyte cryopreservation has gained slow support and acceptance as a viable fertility preservation option [11]. Early experience revealed pregnancy rates ranging from 8 to 33% [12–15]. Freezing oocytes rather than embryos offers the cancer patient obvious advantages [16], particularly for those who do not have a partner for sperm source at the time of cancer diagnosis, or who elect not to use donor sperm. Following cancer treatment, frozen–thawed oocytes can be fertilized with sperm from a future partner or donor, enabling the couple to have a child. Freezing oocytes rather than embryos also avoids the ethical and legal issues surrounding embryo storage and disposal, which is a concern for some patients. In Jennifer's case, oocyte banking was the preferred technique for preserving fertility since she was young, unmarried, and did feel comfortable using donor sperm to bank embryos. Unfortunately, the technique of oocyte freezing is more challenging than embryo freezing and therefore success rates have traditionally been lower. Mature oocytes (MII) are highly sensitive to the freeze–thaw process not only because the oocyte has a large water component making it prone to ice crystal formation but also because the meiotic spindle can depolymerize leading to chromosomal abnormalities and the zona pellucid a can harden leading to fertilization failure [16]. Some of these obstacles have been addressed by using techniques such as vitrification and intracytoplasmic sperm injection.

Until recently, the conventional cryopreservation technique has consisted of slow cooling with differing methods of freezing. However, recent studies suggest that oocyte vitrification may hold greater promise for the future. Vitrification uses higher concentrations of cryoprotectants and rapid cooling techniques (–1,500°C/min) that solidify without the formation of ice crystals. Additionally the rapid fall in temperature throughout the transition phase may reduce the thermal stress to the oocyte [11, 17, 18]. To reduce the toxic exposure of cryoprotectants and prevent extreme dehydration, oocytes are in contact with cryoprotectants for a very short period of time [11, 19]. Initial studies comparing outcomes obtained with the slow-freezing method versus vitrification exhibit a trend toward improved survival, fertilization, pregnancy, and implantation rates, suggesting that vitrification may be a more successful technique [20, 21]. We believe that oocyte cryopreservation is an excellent option for adolescents and unmarried young women undergoing fertility-threatening treatments. Continued research is needed to optimize the success of freezing and thawing of human oocytes so that female cancer patients without a partner can maximize their options for future childbearing.

### Clinical Scenario 2

Marisol is a 38-year-old woman recently diagnosed with Stage 1 estrogen receptor positive breast cancer who also has a recent history of a deep venous thrombosis requiring anti-coagulation. She has been in a serious relationship with a partner for the past 5 years. In discussion with her willing partner, she elected to proceed with a combination of oocyte and embryo cryopreservation. She underwent controlled ovarian stimulation using a letrozole-gonadotropin protocol and banked 11 embryos and 8 oocytes. She received low molecular weight heparin around the time of her oocyte retrieval and transitioned back to warfarin after stimulation.

## Ovarian Stimulation with Aromatase Inhibitors

Invasive breast cancer is the most common neoplasm in women of reproductive age with an estimated 190,000 new cases diagnosed in 2009 [22]. In fact, approximately 25% of women diagnosed with breast cancer in the United States are premenopausal, with 15% under the age of 45 years [23, 24]. In the initial management of breast cancer, surgery is usually followed by adjuvant chemotherapy 4–6 weeks later. Common chemotherapy regimens include an alkylating agent such as cyclophosphamide, which has been found to be highly gonadotoxic. The interval between surgical recovery and chemotherapy often provides sufficient time for ovarian stimulation for embryo or oocyte banking. However, given the potential induction of breast cancer cell proliferation by estrogen [25, 26], there have been theoretical concerns that traditional ovarian stimulation has the potential to cause tumor progression. Therefore, alternative protocols for ovarian stimulation in patients with breast cancer have been under investigation.

Aromatase is an enzyme of the microsomal cytochrome P450 superfamily that catalyzes the rate-limiting step in the conversion of androgens to estrogens in many tissues, including granulosa cells of ovarian follicles [24, 27]. Aromatase inhibitors, such as letrozole, markedly suppress plasma estrogen levels by competitively inhibiting the activity of the aromatase enzyme [28] and can be used successfully as ovulation induction agents. In patients with estrogen receptor positive (ER+) breast cancer, the addition of daily letrozole to gonadotropins in ovarian stimulation protocols significantly decreases serum estradiol levels without affecting oocyte or embryo yield [29, 30]. As demonstrated in the clinical case presented, we have found the letrozole-FSH protocol to be useful in women with breast cancer, particularly ER+ breast cancer, who wish to undergo oocyte or embryo cryopreservation. As with traditional stimulation protocols, most patients can complete their cycles without a significant delay in cancer treatment. Although early studies note that ovarian stimulation with letrozole-FSH is unlikely to cause substantially increased risk of cancer recurrence [24, 31], further follow-up studies with larger sample sizes will be needed to determine whether this protocol has an impact on long-term recurrence or survival in breast cancer patients.

## Combined Embryo and Oocyte Cryopreservation

Since the birth of the first “test tube baby” Louise Brown, in 1978, the techniques of in vitro fertilization have progressively improved to achieve current pregnancy rates of 40–60% [32, 33]. Thus, the most successful option for fertility preservation in women facing cancer is embryo cryopreservation prior to chemotherapy. In fact, the American Society of Reproductive Medicine considers embryo banking the only “standard” procedure for female fertility preservation and should be offered as a first-line option for appropriate patients [34]. Patients diagnosed with early breast cancer represent a group especially appropriate for embryo cryopreservation because the usual 4- to 6-week delay between breast surgery and radiation therapy optimally allows for ovarian stimulation, oocyte retrieval, and embryo freezing. While highly successful, embryo banking for female cancer patients is dependent on a male sperm source, obtained either from partner sperm or from a donor sperm bank. In the case presented, Marisol was in a committed relationship but was not yet married. Because she was not entirely confident about her future with her partner, she elected to cryopreserve both embryos and oocytes. The decision to pursue fertility preservation can be overwhelming for many couples, who are suddenly forced into making a “permanent decision” to create biological offspring together. This no doubt heightens the already intense anxiety that such patients experience as they confront their cancer diagnosis and treatment. As the success of oocyte and ovarian tissue cryopreservation continues to improve, we anticipate that women will have more options available to successfully preserve gametes so that they do not have to make such difficult choices. In the meantime, we feel that it is reasonable to offer appropriate patients the option to bank both gametes and embryos since it offers them greater flexibility for future use.

## Anticoagulation with IVF Stimulation

Patients undergoing controlled ovarian stimulation with exogenous gonadotropin therapy are at risk of thromboembolic events [35], likely due to a hypercoagulable state induced by supraphysiologic serum estradiol levels and subsequent hemoconcentration [36, 37]. Cancer also increases the risk of thrombosis and therefore this population is more likely to require anticoagulation around the time of fertility preservation techniques compared to the general infertility population. Indeed, we have cared for several cancer patients, like Marisol, who have required therapeutic anticoagulation during ovarian stimulation. While there is limited data on the safety of anticoagulation in the setting of IVF, available published reports are reassuring. For example, Yinon et al. reported no bleeding or thromboembolic complications in 24 women undergoing 73 IVF cycles concurrently treated with gonadotropins and daily low molecular weight heparin (LMWH) at a dosage of 0.6–1 mg/kg/day. The last dose was administered 14–16 hours prior to oocyte retrieval and resumed 12 hours after the procedure [38]. Generally, we have converted patients to twice daily therapeutic low molecular weight heparin 1 week before the anticipated retrieval data and instruct the patient to take her last dose of medication 24 hours prior to the procedure. Low molecular weight heparin is initiated 12 hours following the retrieval and conversion to warfarin may begin. Because cancer patients undergoing embryo or oocyte banking may require anticoagulation during stimulation, it is important for clinicians to be aware of such anticoagulation protocols that have been used successfully in clinical practice.

### Clinical Scenario 3

Michelle is an 18-year-old patient with newly diagnosed Ewing's sarcoma requiring high-dose cyclophosphamide and ifosfamide who was referred for fertility preservation given her young age and planned gonadotoxic therapy. According to her oncologist, the patient had a highly aggressive tumor and it was recommended that she undergo immediate cancer treatment. She was extensively counseled about her options including embryo, oocyte, and ovarian tissue banking. She wished to proceed with ovarian tissue cryopreservation and understood that this was an experimental procedure with the potential for future use if the scientific possibilities advanced.

## Ovarian Tissue Cryopreservation

Rather than freezing individual oocytes or embryos, biopsy of the ovarian cortex represents a more efficient way of preserving thousands of primordial follicles at one time. Ovarian biopsies obtained laparoscopically are dissected into small fragments and cryopreserved. As illustrated in Michelle's case, this technique is particularly attractive for girls and single women without a partner and those who cannot delay cancer treatment in order to undergo ovarian stimulation and egg retrieval. In addition, for prepubertal girls, ovarian tissue banking may be the only acceptable method to preserve fertility since ovarian stimulation is not an option [39].

While it might someday be possible to mature oocytes in vitro to achieve pregnancy, autotransplantation of cryopreserved tissue for in vivo oocyte maturation and subsequent IVF appears to be the most promising technique [40]. Ovarian transplantation involves the removal and cryopreservation of ovarian tissue before treatment and the reintroduction of tissue after treatment, either orthotopically or heterotopically, such as in muscle or subcutaneously [41]. Autotransplantation of cryopreserved ovarian tissue also has the potential benefit of restoring temporary endocrine function to cancer survivors who develop premature ovarian failure [42]. In humans, there have been several case reports of ovarian tissue autotransplantation for restoring fertility [43, 44]. In 2004, Donnez et al. reported the first liveborn from orthotopically grafted ovarian tissue fragments to a woman 3 years following chemotherapy and radiotherapy for stage IV Hodgkin's lymphoma [44]. In 2005, another case report was published of a full-term pregnancy following orthotopic autotransplantation of thawed ovarian strips to the cortex of in situ, non-functioning ovaries of a patient with 24 months of ovarian failure following high-dose chemotherapy for Hodgkin's lymphoma [45]. While such reports are exciting, clearly more success must be demonstrated with this technique before ovarian tissue cryopreservation can be considered a realistic option for women faced with cancer.

Similar to oocyte cryopreservation, ovarian tissue cryopreservation is limited by significant technical challenges. First, many oocytes are lost as a result of the freeze–thaw process, but also as a result of initial tissue ischemia at the time of biopsy [46]. Second, the optimal transplantation site has not yet been determined as heterotopic ovarian grafts appear to stimulate differently than expected in traditional IVF. Also, hormone profiles appear different in autotransplanted ovaries as compared to normal ovaries even though neo-vascularization of the ovarian grafts occurs in approximately 1 week and estradiol, FSH, and LH levels revert to premenopausal levels between 3 and 7 months [42, 47]. Perhaps temperature or vascular properties of the heterotopic locations, or the cryopreservation process itself give these grafted ovaries distinct endocrine and oocyte maturation characteristics. Finally, the transplants have short-lived hormonal function, with reports between 9 months and 3 years [48], some even requiring repeat transplantation [49] to maintain function.

Another relevant issue surrounding ovarian autotransplantation is the risk of reseeding cancer to the survivor. Although this phenomenon was not seen when ovarian tissue from lymphoma patients was grafted onto immunodeficient mice [41], the risk is not yet known in humans, and must factor into patient counseling. Currently, the only manner of screening these samples is by conventional microscopic examination of biopsied samples, which is merely an incomplete representation of the entire specimen to be cryopreserved. While many questions remain to be answered with respect to ovarian tissue banking, this option presents a promising experimental technique that is appropriate for some patients.

### Clinical Scenario 4

Ann is a 34-year-old woman with a history of recurrent Hodgkin's lymphoma who was interested in learning about her options for fertility preservation. She was in a committed relationship and was scheduled to undergo high-dose radiation of the left groin for residual pelvic disease. After reviewing her options, she elected to bank embryos using her partner's sperm. Because her ovarian reserve was impaired from prior chemotherapy with a basal FSH level of 14 mIU/ml, she underwent ovarian stimulation with maximum doses of gonadotropins and was only able to bank three embryos. After embryo banking, she sought additional methods of fertility preservation and elected to proceed with ovarian tissue banking and ovarian transposition. Ten days after egg retrieval, she underwent laparoscopic left ovarian transposition and banked a biopsy of ovarian cortical tissue. She recovered well from the procedures and proceeded with her cancer treatment.

## Gonadotoxicity of Cancer Therapy

Ann's case highlights the damaging effect of cancer therapy on the ovaries and the challenges that exist when attempting ovarian stimulation after cancer treatment. The ovary is particularly sensitive to the adverse effects of cancer treatments because of the finite number of germ cells present in the post-natal ovary [50, 51]. Reproductive lifespan is determined by the size of the follicular pool and therefore, cancer treatments that cause follicular depletion are thought to accelerate the onset of menopause [52]. Large retrospective cohort studies assessing menstrual function post-chemotherapy have clearly demonstrated that cancer survivors are at risk of both acute and long-term ovarian failure [53, 54]. The irreversible gonadotoxic effects of some of the chemotherapeutic agents are well documented, particularly for alkylating agents, such as cyclophosphamide, busulfan, and ifosfamide, common components of polychemotherapy for sarcomas, leukemia, lymphomas, and breast cancer [55, 56]. Pelvic radiation therapy is also known to cause follicular destruction followed by reproductive dysfunction [53, 54, 57, 58]. Exposure to 6 Gray of pelvic radiation appears to be toxic to oocytes and many women experience premature ovarian insufficiency [59, 60]. Ovarian failure from these agents appears to be dose-related and the effect is dependent on age at the time of treatment [55, 61]. As seen in Ann's case, even before menstrual dysfunction occurs, cancer survivors have evidence of impaired ovarian reserve compared to similarly aged controls [62–66]. We have observed that the response to ovarian stimulation is often reduced in cancer survivors, yielding fewer oocytes and embryos. Although it is not always possible to predict a patient's response to ovarian stimulation with accuracy, the patient's age, measures of ovarian reserve, and treatment history (type, cumulative dose, and duration of treatment) are important factors to consider when planning fertility preservation strategies in cancer survivors scheduled to undergo additional gonadotoxic therapies.

## Ovarian Transposition

Ann's case also helps to draw attention to ovarian transposition as an important fertility-preserving procedure that is appropriate for selected patients. Oophoropexy and ovarian transposition are surgical procedures that secure the ovary in a fixed anatomic position outside of the radiation field and can be an option for preserving gonadal function in patients undergoing pelvic radiation. Proper surgical technique of transposition is critical to the successful preservation of ovarian function. Pregnancy rates after this procedure was performed in cancer patients less than 40 years of age and have been reported to range from 60 to 89% [67–69, 70]. Ann was a particularly good candidate for this option because she required radiotherapy to the groin. After discussing the proposed radiation treatment with her radiation oncologist, it was clear that her left ovary would be significantly damaged by this treatment. Therefore, to help protect the ovary from radiation exposure, she elected to have a laparoscopic ovarian transposition procedure in which the ovary was moved to the level of the iliac crest.

## Selecting More than One Fertility Preservation Option

It is important for the clinician to recognize that fertility preservation techniques are not mutually exclusive, and some patients may be good candidates for pursuing multiple options. For example, in the case presented, Ann not only completed embryo banking, but also banked ovarian tissue and had ovarian transposition surgery. In some cases, patients may elect to pursue multiple options because of poor response to stimulation, or inadequate numbers of oocytes or embryos banked. Others may simply wish to expand their future reproductive options, anticipating continued advancements in reproductive technologies. For example, even a woman who successfully freezes embryos may elect to preserve ovarian tissue in the hopes that the many follicles present in the tissue will provide additional opportunities for having children in the future. Laparoscopic surgery to move an ovary away from the radiation field represents an ideal opportunity to remove and bank ovarian tissue at the same time [69]. It must be recognized that multiple procedures may present additive risk which must be carefully balanced with the potential long-term benefit to the patient. Each clinical situation will present unique opportunities and challenges for fertility preservation and it is important to offer a range of options to patients. Sometimes the best option is not feasible, and alternative, less successful options must be pursued.

## Conclusions

Fertility preservation ranks as one of the greatest concerns for women and girls diagnosed with cancer and as technological advancements in the field occur, more patients are pursuing fertility preservation than ever before. Consequently, physicians in the discipline of oncofertility must be keenly aware of the diverse clinical situations that occur in this field. The clinical scenarios presented in this chapter provide just a glimpse of the complex circumstances confronting the reproductive endocrinologist caring for cancer patients. We have found that a variety of techniques can be used to minimize the risk and maximize fertility preservation options for these patients. It is important to individualize care and be flexible about specific protocols and fertility preservation options. Because of the sensitive and urgent nature of oncofertility, we recommend a team approach to patient counseling. Ideally if time permits, patients meet with physicians, nurses, and mental health professionals in order to discuss fertility preservation options over several visits. This allows for a more comprehensive evaluation to explore and understand the psychosocial and medical needs of each patient. Helping patients navigate fertility preservation options can be incredibly gratifying since it gives patients some control of their reproductive options and provides hope for a “normal life” in the future. We are confident that advancements in the field of oncofertility will continue to expand the reproductive options of all cancer patients.

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# Chapter 6
# Cancer Genetics: Risks and Mechanisms of Cancer in Women with Inherited Susceptibility to Epithelial Ovarian Cancer

**Lee P. Shulman and Jeffrey S. Dungan**

## Introduction

In the foreword to the first book on oncofertility by Woodruff and Snyder, the authors stated that oncofertility bridges traditional areas of basic science and medical science to provide reproductive options to young people who survive life-preserving but fertility-threatening treatments for cancer. A part of this cohort of reproductive-aged women also includes those who are "previvors": specifically, women at increased risk for malignancies for who prevention may entail interventions that can adversely affect their ability to conceive and carry a pregnancy. However, women who are at increased risk for ovarian cancer based on family history or the presence of genetic mutations that predispose them to develop ovarian cancer at a higher frequency and younger age than is typically observed in the general population face not only a highly lethal malignancy but also interventions that temporarily or permanently prevent them from having children. So while preventive and therapeutic interventions for other malignancies can adversely affect the ability of affected women to reproduce, epithelial ovarian cancer (EOC) is unique in that for the highest risk women, preventive interventions should usually occur during the reproductive years, and that the most effective prevention involves ovarian extirpation, removing the capacity to produce biologic offspring. Nonetheless, advancements described throughout this book have given promise to these very women.

Epithelial ovarian cancer is associated with profound morbidity and high rates of mortality for which no effective screening protocol has yet been developed. It is important to recognize that most epithelial ovarian cancers occur in postmenopausal women with no noteworthy family history and no detectable deleterious gene mutations; indeed, genetic alterations are not even detected in the majority of women who develop *premenopausal* ovarian cancer. Nonetheless, the presence of mutations

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in specific genes, most commonly BRCA1 and BRCA2, will predispose women to develop ovarian cancer at a markedly higher frequency and younger age not commonly observed in the general population. While there is little doubt that perturbations of other genes are responsible for the development of ovarian cancers and other solid tumors, our current knowledge of the "oncogenome" relevant to EOC is somewhat limited to several genes that have been associated with the development of ovarian tumors and malignancies.

There are effective preventive approaches for reproductive-aged women at increased risk for developing epithelial ovarian cancer; however, these are invariably associated with either fertility delay (oral contraceptives) or permanent infertility (tubal ligation, bilateral salpingoophorectomy). As such, the identification of reproductive-aged women at the highest risk for developing ovarian cancer must entail a discussion of these preventive approaches and should include a frank discussion of family planning and fertility preservation for those women seeking to become pregnant.

Our knowledge of the oncogenome continues to expand and provide important information for delineating mechanisms of tumorigenesis that are of considerable value in the development of effective preventive, screening, diagnostic, and therapeutic protocols. In this way, oncofertility provides a bridge from basic science to clinical practice that can empower reproductive-aged women to conceive despite undergoing interventions chosen to prevent or treat malignancy. To familiarize readers with those genetic findings that increase a woman's likelihood of developing ovarian cancer, this chapter will provide a review of the disease and genomic epidemiology of EOC and genetic mechanisms associated with a predisposition to the development of epithelial ovarian cancer.

## Epithelial Ovarian Cancer

Most ovarian malignancies are epithelial in nature and are characterized by differing histological subtypes including serous, mucinous, endometrioid, and clear-cell tumors. While cervical cancer remains the most common cause of gynecologic cancer death worldwide, EOC is the leading cause of death from gynecologic malignancy in the developed world. It is estimated that EOC is diagnosed in approximately 200,000 women worldwide and results in the deaths of 120,000–130,000 women each year [1]. In the United States, there are approximately 22,000 new cases of ovarian cancer diagnosed, with more than 15,000 deaths attributed to EOC annually [2]. One reason for this difference in causes of gynecologic cancer death in the industrialized and developing world is that EOC usually does not present with unique symptoms that would indicate the presence of an early malignancy, such as what occurs with bleeding per vagina and endometrial cancer. Additionally, there is as yet no effective screening algorithm to identify women with early ovarian cancer, as is available worldwide with the Papanicolau smear and cervical dysplasia and cancer. While early stage EOC is associated with generally good clinical outcomes, most ovarian cancers (approximately 70%) are unfortunately detected at a more advanced stage and are associated with generally poor survival rates despite continuing advancements in surgical techniques and chemotherapy regimens [3].

In addition to the lack of unique associated symptoms and an effective screening protocol, no specific patient characteristics (e.g., obesity and endometrial cancer) or lifestyle issues (multiple sexual partners and cervical cancer) are strongly associated with the development of EOC. Nonetheless, reproductive history does provide some information in assessing a woman's risk for developing EOC. Nulliparous women in the general population are at a higher risk for developing EOC than those women who have been delivered of children. The birth of the first child reduces one's risk for developing EOC by 45%, with each additional pregnancy further reducing that risk by 15% for each pregnancy [4]. However, this reduction in risk for developing EOC in the general population is not observed among women with certain predisposing gene mutations (BRCA); indeed, the risk for EOC in BRCA mutation carriers paradoxically appears to increase with the number of children [5]. Risk reduction for EOC in the general population is also observed among women who breastfeed their infants [6].

Family history of EOC is the strongest risk factor associated with an increased likelihood for developing EOC (outside of the hereditary cancer syndromes). A woman with a first-degree relative (e.g., mother, sister, daughter) with EOC will have her risk increased two- to threefold (1.5–4%) while two affected relatives will increase a woman's risk fivefold to 7% [7, 8]. An additional factor in assessing risk in women with a family history of EOC is the age at diagnosis; Auranen and colleagues [9] showed that affected relatives with a diagnosis of EOC before the age of 55 conveyed a higher risk than those relatives with EOC diagnosed after the age of 55.

Despite there being no effective screening modality yet developed for EOC, risk reduction can be achieved by high- and low-risk women. Oral contraceptive (OC) use has been shown to reduce the risk of developing EOC in all women regardless of their underlying risk strata; the longer the use, the greater the preventive effect [5]. More recent studies not only confirm this beneficial effect of OCs, but show that more modern pills exert a similar risk reduction to that observed with older and higher dosed pill regimens [10]. In most studies, the use of OCs in BRCA mutation carriers does not appear to be associated with a consistently increased risk for developing breast cancer [11]. Other interventions that have been associated with risk reduction include breast feeding, tubal ligation, and bilateral salpingoophorectomy (BSO) [5]. All of these interventions, including OCs, are associated with an inability to conceive, with tubal ligation and BSO associated with permanent sterilization. For reproductive-aged women seeking future childbearing, consideration of the timing of future pregnancies is thus critical in the choice of a risk-reducing intervention. While the removal of the tubes and ovaries is associated with the most profound reduction in risk, BSO is the one approach that prevents any possible future childbearing (assisted reproductive technologies can be used by women who have undergone tubal ligation) and when done before the onset of menopause, it is associated with an increased risk for premature cardiovascular morbidity and all-cause mortality if postoperative estrogen therapy is not initiated [12, 12A].

## Heritable Cancer Syndromes and EOC

The majority of EOC cases occur in women without a family history, indicating an increased risk. However, approximately 5–10% of EOC cases are associated with the inheritance of genes that predispose individuals to develop EOC. The delineated hereditary cancer syndromes involving EOC include breast/ovarian syndrome, site-specific ovarian cancer syndrome, and Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer, or HNPCC syndrome). These cancer predisposition syndromes are the result of the autosomal dominant transmission of highly penetrant germline mutations in tumor-suppressing genes. The inheritance of a mutated copy of one of these genes not only conveys a markedly increased risk for developing EOC but also increases the likelihood of developing the malignancy at a far younger age than is usually observed in the general population. It is this characteristic of hereditary ovarian cancer that profoundly impacts the woman found to be a carrier of an inherited mutation in a tumor-suppressing gene and leads many to the consideration of risk reducing interventions that impact the ability to conceive and may preclude the possibility of any future pregnancies.

## Genetic Mechanisms

The increased risk for developing cancer in women with mutations in cancer susceptibility genes invariably begins with the inheritance of a germline mutation from either parent. While EOC can only occur in females, genes that predispose to the development of EOC are autosomal in nature and thus can be inherited from either parent. This concept is critical with regard to family history information as both parents can transmit gene mutations; accordingly, obtaining careful family histories of an individual's maternal and paternal families is paramount to developing an accurate risk assessment.

By definition, this germline mutation is present at conception and thus every cell of the individual will have the gene mutation, a fact likely associated with the multiorgan effect of many cancer susceptibility genes. Nonetheless, the inheritance of a cancer susceptibility allele is only the *first* step in promoting the development of EOC. Its mere presence does not guarantee that an individual with an inherited susceptibility gene mutation will go on to develop EOC.

The development of EOC, as well as other heritable cancers, depends on the occurrence of a *second* step [13]. That an individual has inherited the first "step" serves to explain why such individuals have a higher risk for developing cancer than the general population and that the malignancy usually occurs at a younger age and why it is more likely to occur bilaterally than in the general population.

Cancer is a disease of somatic cells; however, if two (or more) events are needed for the cells to become malignant, then inheriting the first step, as opposed to waiting for it to occur through environmental impact, will surely increase the likelihood of it occurring compared to those who do not inherit such mutations. The second (and any subsequent) step is invariably somatic in nature, also explaining why not everyone who inherits a susceptibility gene develops the malignancy. Molecular studies of cancers in individuals with malignancies arising from hereditary cancer syndromes frequently show a loss of heterozygosity at the genomic position of the tumor suppressor gene in tumor tissue. The loss in heterozygosity is the second step in the development of malignancies in individuals who have inherited mutated susceptibility genes.

There are numerous mechanisms that likely lead to this loss of heterozygosity and, thus, inactivation of the tumor suppressing gene. While such cellular and nuclear events are common and widespread mechanisms and are mostly random processes by which genes and chromosomes are deleted, replaced, or rearranged, in the presence of an inherited gene mutation, such events can lead to the inactivation of tumor-suppressing gene function and predispose that organ to undergo malignant transformation. In such cases, this process is known as biallelic inactivation. Inherited biallelic mutations are exceedingly rare and present with a different clinical presentation than that described with monoallelic (dominant) inheritance.

It is interesting to note that while most hereditary cancer syndromes, including EOC, are mostly transmitted in and present as a classic autosomal dominant inherited condition, the requirement of a second step that inactivates both alleles (biallelic inactivation) makes the cellular mechanism necessary for the promotion of tumorigenesis to be recessive in nature.

## Heritable Cancer Syndromes and EOC

### *Hereditary Breast and Ovarian Cancer (HBOC)*

Hereditary breast and ovarian cancer syndrome (HBOC) is characterized by families with multiple members with breast cancer and EOC, with most such families having more cases of breast cancer than ovarian cancer. HBOC families, like other families with hereditary cancer predisposition syndromes, are characterized by a far earlier age of onset than is seen in the general population, as well as a higher likelihood of bilateral disease. In addition, HBOC families have a markedly higher frequency of family members with breast cancer and EOC occurring in the same individual and for some gene mutations, a strikingly higher risk for breast cancer in men.

The majority of families with HBOC have inherited mutations in two tumor-suppressing genes, BRCA1 and BRCA2. A recent study by Ramus and colleagues [14] showed that 81% of families with at least two cases of EOC and one case of breast cancer had a deleterious mutation in BRCA1 or BRCA2, thus confirming earlier studies and models demonstrating that the majority of cases of HBOC are associated with BRCA1/2 mutations [15].

BRCA1 is located on chromosome 17q21, contains 22 coding exons, and spans 80 kb DNA (Fig. 6.1), whereas BRCA2 is located on chromosome 13q12-13, contains 26 coding exons and spans 70 kb DNA (Fig. 6.2). Both genes are part of the DNA break repair pathway and appear to function as tumor-suppressor genes, with mutations resulting in highly penetrant susceptibility to EOC and breast cancer. Mutations of BRCA1 and BRCA2 associated with the development of EOC and breast cancer are found throughout the coding regions and at splice sites. Most of these mutations are small insertions or deletions that lead to frameshift mutations, nonsense mutations, or splice site alterations [16], all of which lead to premature protein termination and altered or absent proteins. In addition to these mutations

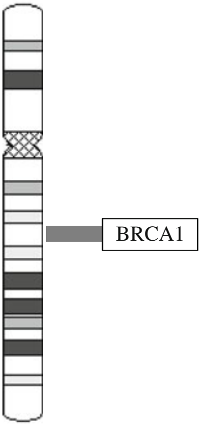

**Fig. 6.1** BRCA1 locus on chromosome 17

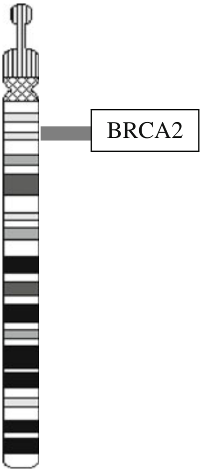

**Fig. 6.2** BRCA2 locus on chromosome 13

and some missense mutations, large deletions and rearrangements not detectable by standard PCR have been identified and are now part of the molecular testing provided to those undergoing BRCA analysis. Indeed, these large genomic alterations have been found to be relatively common in some populations from central Europe and the US [17]. As BRCA1 and BRCA2 are autosomal genes with high penetrance, transmission can occur either maternally or paternally; accordingly, equal attention must be paid to the paternal relatives of a woman being evaluated for a possible BRCA mutation. BRCA1 mutations do not frequently result in increased risk for cancer in men, whereas BRCA2 mutations increase the risk for male breast cancer; nonetheless, the relative dearth of paternally based malignancies must not deter one from considering a paternally transmitted BRCA mutation. Kessler and colleagues (Personal communication) found that among individuals at increased risk for heritable colon cancer, an equal distribution of paternal and maternal transmission of deleterious (and autosomal) genes was found. However, among individuals at increased risk for HBOC, an approximately 70/30 (maternal to paternal) distribution was delineated. This is despite the fact that genes causing HBOC are autosomal and thus should be equally distributed between paternal and maternal lines of transmission. While those families with either few members or few females pose a challenge in counseling, as affected females provide the main evidence of the existence of a deleterious BRCA mutation, this perceived skewing of parental transmission shows that in many cases, affected females in the paternal lineage are either ignored or not considered on an equal status with affected members from the maternal lineage. This may occur because of a misperception that HBOC is a disease of women and that genetic events in paternal families do not play an important role.

The frequency of BRCA1 or BRCA2 mutations in the general population is estimated to be 1/300 to 1/800 [18]. BRCA mutations are found in approximately 6–8% of EOC cases, but in 80–90% of hereditary breast-ovarian cancer syndrome [2]. However, some populations and communities have a higher frequency of BRCA mutations than is found in the general population. In the United States, BRCA mutations are found in approximately 1 of every 40 individuals of Eastern European (Ashkenazi) Jewish ancestry, a frequency far higher than the general US population. What also distinguishes this community is that three mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) account for approximately 98% of mutations detected. In Iceland, the 999del5 mutation in BRCA2 accounts for approximately 7% of all cases of EOC occurring in Icelanders. These mutations are known as “founder mutations,” so named because in certain populations begun by a small ancestral group initially isolated by societal behavior or geography, certain genes in the original “founders” of a population can become far more common in succeeding generations than would occur in the general population.

The identification of founder mutations allows for more facile screening of individuals of those groups associated with founder mutations. As such, evaluating individuals of Eastern European Jewish ancestry for a BRCA1 or BRCA2 mutation is now accomplished by first determining the presence of one of these three mutations, unless previous analysis of an affected relative revealed a different (non-founder) BRCA mutation associated with breast or ovarian cancer. However, even in some of these situations, a "single site" analysis would potentially be augmented with a founder mutation analysis if the family history indicates that another mutation may be present. If testing for a founder mutation is found to be negative, then gene sequencing and rearrangement analysis should be offered to provide a complete and thorough molecular evaluation.

BRCA1 mutations appear to confer a higher risk for developing EOC than BRCA2 mutations. Satagopan and colleagues [19] found that carriers of either of the two BRCA1 founder mutations in the Ashkenazi Jewish population (185delAG and 5382insC) were estimated to have a 37% risk for developing EOC by the age of 70, whereas those carrying the founder BRCA2 mutation (6174delT) were estimated to have a 21% risk. Mutations of either BRCA gene are associated mostly with the development of serous epithelial ovarian cancers, as opposed to mucinous or other histologic subtypes. Of interest is that the risk for developing breast cancer among carriers of all three founder mutations is similar and estimated to be approximately 85% by the age of 70.

## *Site-Specific Ovarian Cancer*

Site-specific ovarian cancer syndrome is not associated with a single susceptibility gene; rather, it is a term used to describe families with several first- and second-degree relatives with EOC. In actuality, it is used to describe families with several relatives with EOC, but with no relatives with breast cancer, endometrial cancer, colon cancer, or any of the other malignancies associated other hereditary cancer syndromes. While it is unlikely that site-specific ovarian cancer syndrome is caused by a gene or genes not yet identified, it may be a variant of a recognized heritable cancer syndrome, meaning that EOC either presents prior to the other associated malignancies or is representative of a genetic variant presenting with an overwhelming predominance of EOC over other malignancies.

In many of the families, site-specific ovarian cancer syndrome may appear to be transmitted in a dominant fashion. However, Stratton and colleagues [7] estimated the risk of EOC in such families to be 5%, considerably less than the 50% associated with a dominantly inherited condition. However, this same group [20] later estimated the risk to be higher, concluding that even when a BRCA mutation is not detected, that the prevailing risk model explains that most cases of familial EOC are associated with BRCA mutations, with the others attributed to sporadic clusters and issues of sensitivity of the mutational assays.

Regardless of whether the site-specific ovarian cancer syndrome is a variant of the HBOC or Lynch syndrome, or represents the phenotypic expression of susceptibility genes different from those that cause HBOC or Lynch syndrome, patients from such families carry increased risk for the development of EOC and should be offered ongoing evaluation and preventive interventions similar to that provided to women from families known to have a recognized cancer susceptibility genetic syndrome.

## Lynch Syndrome

Colon cancer is the preeminent malignancy of this hereditary cancer syndrome, previously known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome. Indeed, Lynch syndrome (previously divided into Lynch I or Lynch II) is the most common cause of hereditary colorectal cancer. As with other cancer susceptibility syndromes, Lynch syndrome is associated with an increased risk for cancers in multiple organs including endometrial, urogenital, pancreatic, and biliary tract and EOC. Of note is that more recent study of Lynch families shows that female members of these families have a higher cumulative lifetime risk for developing endometrial cancer than for developing colorectal cancer [2].

Lynch syndrome is a result of gene mutations in the multistep mismatch repair system (MMR). MMR genes are located on five different chromosomes and encode for proteins that recognize and repair damage in the DNA that leads to DNA mismatches. One complex of proteins consisting of the protein MSH2 combined with MSH6 or MSH3 recognizes the DNA mismatch and binds to the site. An inactivating mutation of MSH2 blocks the ability to recognize a DNA mismatch negating the function of this complex. Mutations of either MSH6 or MSH3, on the other hand, may not have a similar deleterious effect as these two proteins have overlapping functions and thus an inactivating or adverse mutation in one may not adversely affect the function of the overall MMR system. Once the mismatch is recognized, MLH1 (with PMS1 or PMS2) then provides the necessary steps to resynthesize the DNA strand in its original and correct sequence. A total of seven MMR enzymes have been delineated and mutations in each of the seven genes have been identified (Table 6.1) [21]. Mutations in the MLH1 and MSH2 genes are the most common and account for approximately 90% of observed mutations, followed in frequency by mutations in MSH6 and PMS2. Mutations in the remaining three genes are rarely observed in Lynch syndrome families.

**Table 6.1** Genes associated with mismatch repair system

| Gene name | Frequency in Lynch pts | Chromosome locus |
|---|---|---|
| MLH1 | 40–45% | 3p21.3 |
| MSH2 | 40–45% | 2p22-p21 |
| MSH6 | 7–10% | 2p16 |
| PMS1 | unknown | 2q31-q33 |
| PMS2 | <5% | 7p22 |
| MSH3 | 0 | 5q11-q12 |
| MLH3 | 0 | 14q24.3 |

The type of MMR mutation provides important information as to the risk for developing a particular malignancy in women with Lynch syndrome mutations. Watson et al. [22] reported that the risk for EOC was significantly higher in families with MSH2 mutations compared to families with MLH1 mutations. Analogously, Wijnen et al. [23] found that women carrying MSH6 mutations were twice as likely to develop endometrial cancer as women who carried MSH2 or MLH1 mutations.

It was surmised that the genetic mechanism for the increased risk for carcinogenesis in cases of MMR gene mutations was similar to that of BRCA mutations; namely, that dominant inheritance of a mutation provided for the germinal “first-step” and that a second somatic step led to the loss of the normal or “wild-type” co-allele and that this loss of heterozygosity eventually promoted the cellular aberration that resulted in malignant transformation of the cell and, eventually, organ. However, Aaltonen and colleagues [24] found no loss of heterozygosity at a locus coinciding with the MSH2 site on chromosome 2 linked to colorectal cancer in 14 cases from 3 families, suggesting a cellular mechanism different from the conventional mechanism attributed to biallelic inactivation and alteration of tumor-suppressing gene function in the development of tumors. Another explanation for the findings by Aaltonen and colleagues is that the MMR gene mutation, without the loss of heterozygosity, adversely affects the DNA mismatch repair mechanism, leading to a “domino-like” dysfunctional cascade on those cellular mechanisms responsible for proper growth and function. Perhaps the surprising findings of no loss of heterozygosity in Lynch colorectal cancer cases indicates that the genes being disrupted in the Lynch syndrome are those genes responsible for maintaining the proper DNA sequence and that adversely affecting their function, even with a only single allele and the maintenance of the wild-type allele, may be sufficient to initiate abnormal cellular and nuclear processes that lead to carcinogenesis.

These inactivating mutations not only prevent the repair of damaged DNA but also increase the rate of mutations at the DNA microsatellites of growth-regulating genes. Microsatellites are short (1–5 base pairs), polymorphic DNA sequences that are repeated 15–30 times at a given locus and distributed throughout the genome. Microsatellite instability (MSI) thus serves as a marker for MMR mutations; indeed, analysis for microsatellite instability or immunohistochemical (IHC) staining is the first diagnostic step in determining the presence of a DNA repair defect for many individuals at increased risk for MMR mutations. IHC can evaluate tumor tissue for the presence or absence of the proteins MLH1, MSH2, MSH6, and PMS2 but cannot assess the functionality of any of these proteins. As such, IHC cannot determine whether the protein present does not function properly because of a missense mutation and thus cannot definitively identify the gene with the mutation; accordingly, IHC should be combined with MSI to screen prospective tumors for MMR mutations. MSI is a common feature of Lynch-associated tumors; however, studies of MSI in ovarian tumor tissue from EOC have not provided consistent diagnostic correlation.

Although mutations of BRCA1/2 account for the majority of cases of hereditary EOC, Lynch syndrome mutations account for a small proportion of all cases of EOC [25]. Ovarian cancers associated with BRCA mutations are mostly serous in nature; conversely, MMR mutations are associated with a variety of ovarian cancer histologies including endometrioid and clear-cell cancers.

Assessing a family for Lynch syndrome is accomplished by determining whether the history meets Amsterdam II criteria (see Table 6.2). If a family history is suggestive of Lynch syndrome but the criteria cannot be met because of family size or other factors, consideration of risk can be accomplished using revised Bethesda criteria

**Table 6.2** Amsterdam II criteria for Lynch syndrome

At least 3 relatives with an HNPCC cancer:
Colorectal, endometrial, stomach, ovary, ureter/renal pelvis, brain, small intestine, hepatobiliary tract, or sebaceous tumor of skin
AND:
(1) One is a first-degree relative of the other 2
(2) At least 2 successive generations affected
(3) At least 1 of the HNPCC cancers was diagnosed at <50 years of age
(4) Familial adenomatous polyposis has been excluded

(Table 6.3). Women with Lynch mutations do not have an associated increased risk for developing breast cancer; as such, family histories with multiple family members with ovarian cancer and no cases of breast cancer, but having family members with Lynch-associated malignancies (e.g., colorectal cancer, endometrial cancer) should first be evaluated for MMR mutations rather than BRCA mutations [26].

**Table 6.3** Bethesda guidelines to determine which colorectal tumors should undergo MSI testing

(1) Colorectal cancer diagnosed in a patient <50 years old
(2) Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumor, regardless of age
(3) Colorectal cancer with the MSI-H histology diagnosed in patient <60 years old
(4) Colorectal cancer or HNPCC-tumor diagnosed <50 years old in at least one first-degree relative
(5) Colorectal cancer or HNPCC-associated tumor diagnosed at any age in 2 first-degree or second-degree relatives

Individuals who do meet Amsterdam II criteria are evaluated by obtaining peripheral blood for direct sequencing of the MLH1 and MSH2 genes. For those individuals whose families do not meet Amsterdam criteria but do meet Bethesda criteria, first evaluating tumor tissue for MSI and IHC (before mutation testing) is the preferred approach for screening at-risk individuals. This approach is associated with high (90–95%) sensitivity for detecting MMR gene mutation carriers, but as with IHC, provides no information as to which gene is mutated and thus which malignancy that individual may have the highest risk for developing.

The lifetime risk for developing EOC in women with a Lynch syndrome mutation is approximately 12%, a tenfold increase over the general population risk (1–1.5%) but less than the risk associated with BRCA1/2 mutations. Interestingly, while most cases of ovarian cancer in Lynch syndrome families are malignant epithelial tumors, most are well or moderately differentiated and are FIGO Stage I or II at the time of diagnosis. This is in sharp contradistinction to BRCA mutation-associated tumors, which tend to present in a more advanced stage and be more poorly differentiated. Most of the Lynch families with EOC who were studied were found to have germline mutations of the MLH1 or MSH2 genes [27]. However, Cederquist and colleagues [28] reported a high frequency of a variety of EOC in Swedish women with MSH6 mutations, with an estimated 33% lifetime risk of developing EOC in this Swedish cohort. As with other cancer susceptibility genes, certain mutations in particular populations may exert a different impact on cancer risk than that typically observed in the general population. However, similar to women with BRCA 1 or 2 mutations, women with Lynch mutations tend to develop EOC at a younger age (5th decade) than sporadic cases of EOC (7th decade).

## Other Genetic Syndromes Associated with EOC

Ovarian cancer is found as an associated malignancy in other genetic syndromes (Table 6.4). Syndromes associated with EOC are rare and are usually associated with non-epithelial ovarian cancer, although some cases of serous and mucinous EOC have been reported. While ovarian cancers and tumors have been reported in women with these genetic conditions, the overall risk for developing ovarian cancer in women with these conditions appears to be similar to that of the general population. Notwithstanding, evaluation of the ovaries by ultrasound or laparoscopy in cases of adnexal masses of women affected by these uncommon Mendelian disorders is clearly warranted.

**Table 6.4** Genetic syndromes associated with ovarian cancer

| Syndrome | Inheritance | Gene (chromosome) | Clinical features | Ovarian cancer |
|---|---|---|---|---|
| Peutz-Jeghers | AD[a] | STK11 (19) | Melanocytic macules (mouth and lips); polyps in GI tract; increased risk of GI tract CA | Sex cord-stromal tumors (SCST); granulosa cell tumors |
| Ollier | Sporadic/AD? | PTHR1 (3) | Multiple enchondromas; Secondary chondrosarcomas; Orthopedic complications | Granulosa cell tumors |
| Gorlin | AD | PTCH (9) | Basal cell ca of the age 30; jaw cysts; vertebral abnormalities | Skin before fibrosarcoma; also benign fibromas |
| Cowden | AD | PTEN (10) | Hamartomatous lesions of skin and organs; macrocephaly; increased risk of breast, thyroid endometrial CA and endometrial cancers | Epithelial ovarian cancer |

[a] autosomal dominant

## Counseling of Women at Increased Risk for Developing EOC

While only a small percentage of ovarian cancers can be attributed to the inheritance of susceptibility genes, identifying those women at risk for inheriting a susceptibility gene is critical in order to provide optimal care and management. Hereditary EOC tends to occur at an earlier age than sporadic cases. Given the lack of an effective screening protocol for EOC, it is important to identify these high-risk women so that prevention and management options can be provided, which typically occurs during a woman's reproductive years. While effective breast screening protocols do exist for women at increased risk for breast cancer, and while some of the preventive interventions for breast cancer can reduce fertility (e.g., tamoxifen and raloxifene), *all* of the preventive measures available to reduce the risk of EOC in high-risk (and low-risk) women involve transitory or permanent inhibition of fertility. Tailoring these interventions that allow a clinician to provide optimal balance reducing the risk of EOC and allowing a woman to maintain her reproductive capacity for as long as she wishes to conceive is a key goal of cancer genetics programs. Conversely, testing the entire population for susceptibility genes is not currently feasible because of economic factors and the relative low frequency of these deleterious genes in the general population. Currently, the most effective tool for determining risk for hereditary EOC and for providing genetic testing is genetic counseling and cancer risk assessment.

The primary care clinician holds the key to effective identification of those individuals at increased risk for hereditable cancers, with a thorough assessment of the family history being the vital component. Individuals with a personal or family history suggestive of a hereditary or familial cancer should be referred for further counseling and cancer risk assessment. This can be performed at a genetics center, oncology center, or any facility that has trained personnel equipped to properly evaluate personal and family histories and perform a cancer risk assessment. Such personnel are, but are not necessarily limited to, genetic counselors, geneticists, oncologists, gynecologists, internists, family medicine providers, nurse practitioners, or other professionals that provide care to those who are at risk for cancer and cancer syndromes and who have the expertise and interest to do so.

In no cases should patients be coerced into undergoing cancer risk assessment or genetic testing. The long-standing tenet of non-directive counseling must be followed when discussing cancer risk with patients and patient autonomy must always be respected. Indeed, counseling should serve to empower individuals to make informed decisions about their health management, not to dictate or mandate individuals to undergo (or forego) certain tests or management options based on the opinions of the counselor or provider. Women who are so identified as being at increased risk for hereditary EOC by their primary care provider may benefit from a thorough and detailed discussion with a specialist about their risk for developing cancer, the screening and testing that is available to refine their actual risk, and the preventive interventions that are available to them, even if they ultimately choose to forego any further evaluation or risk-reducing intervention. In addition to providing information that can reduce morbidity and mortality, such counseling can also address the anxiety and the numerous psychosocial issues that a personal or family history or cancer can induce.

The process and logistics used to identify and refer women who are at increased risk for hereditary cancer syndromes may be hampered by the considerable barriers to such endeavors. Taking a family history involves time, something in short supply for most primary care providers. Even if a complete family history is taken, medical records are needed to confirm the presence of a malignancy that may increase or decrease a woman's risk for developing cancer. "I was told that my grandmother died from stomach cancer" is a familiar statement in our practice. In many instances, medical records actually indicate that it was not "stomach" cancer. Whether it was actually metastatic ovarian cancer or ulcerative colitis would obviously and profoundly impact the cancer risk assessment of the woman. Unfortunately, many of these medical records are not obtainable. For those clinicians who are able to develop detailed family histories, existing written and electronic medical records systems frequently do not facilitate the updating of such family history information. Finally, even if all the proper components are in place, many primary care clinicians do not have the clinical experience to identify ancillary conditions that may herald a cancer predisposition syndrome. While breast and ovarian cancers in a family clearly place a woman at increased risk for those same malignancies, how does thyroid cancer affect that risk? What about colon polyps, or colon cancer? And if there are several cases of endometrial cancer in a family along with cases of breast and ovarian cancer, what would be the best test to offer a patient if the clinician is going to offer testing without referral for more detailed counseling? All of these issues serve to detract from our ability to accurately assess the risk of women with personal and family histories suggestive of an inherited predisposition to cancer development. However, new programs designed to facilitate data collection, such as HughesRiskApps [29], are now available that allow individuals to provide this type of family information outside of the actual face-to-face visit time with their clinician (e.g., waiting room, mammography center). Such systems should allow easily updated and evaluated histories to determine whether there is an increased risk that needs to be addressed with referral, counseling, or testing.

When a woman is referred for further counseling, a specific cancer risk assessment can be performed. While risk models are not available for all malignancies, risk models are available for HBOC and EOC. Risk models take into account a wide spectrum of family risk factors including age of onset, number and relation of affected members, and presence of associated cancers among other personal and disease characteristics. Two types of cancer risk assessment can be performed: a quantitative analysis determines the risk of an individual to be a carrier of a mutated susceptibility gene, and a qualitative analysis based on family history, medical records, and pathology reports, among other documents [30], which determine the risk of the individual to develop cancer. Both approaches to risk determination incorporate family history and medical information, but the endpoints are quite different, and it is incumbent on the provider to be sure the patient understands the difference.

It is again important to emphasize that cancer susceptibility genes are autosomal and thus transmissible by either one's father or one's mother. Attention must be paid to both lineages, with the recognition that families with relatively few females may be difficult to identify as being a family with a cancer susceptibility gene for EOC because of the relatively few individuals with a potential for phenotypic expression (i.e., cancer) of the mutated susceptibility gene.

When genetic testing is decided upon, it is optimal to test the affected family member(s) as such individuals are most likely to possess deleterious mutations. Obviously, this is not always possible. In such cases, testing those family members who are most closely related to those affected members is appropriate. However, one should be aware that such testing is not always possible and testing individuals who are neither affected nor closely related to affected members may be appropriate. Indeed, in some cases family members who are either affected or are closely related to affected relatives may choose not to test or choose to not release test results, requiring less closely related family members to get testing to determine their mutation status.

## Conclusions

Epithelial ovarian cancer remains a highly lethal malignancy, primarily as result of our inability to detect early, and more treatable, EOC lesions. While most cases of EOC are not associated with a family history and appear to be random event with some risk modification from one's reproductive history and exposure to sex steroids, a small percentage of cases are associated with a familial susceptibility to EOC. Such cases are likely to occur bilaterally and develop earlier in life than EOC in the general population, making the identification of such individuals an important priority given the lack of unique and novel symptoms of early stage (and more successfully treatable) EOC. However, until an effective screening algorithm is available, analysis of family history and cancer risk assessment will remain the main tools to assess one's risk for developing EOC.

Identifying those women who carry an increased risk for developing EOC allows them to initiate preventive measures to reduce their risk for developing EOC. Because these measures either temporarily or permanently reduce or eliminate the ability to conceive, appropriate counseling of such women regarding their plans and desires for reproduction is necessary. In this regard, the identification of high-risk women through family history and genetic testing also brings into the process the consideration of novel reproductive technologies that may allow women to reproduce or conceive even when electing to initiate preventive measures. Oncofertility counseling and interventions for reproductive-aged women at increased risk for EOC are thus important for providing effective overall care to these women and provide the potential for reproduction for women seeking EOC prevention with contraceptive measures.

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# Chapter 7
# Protecting and Extending Fertility for Females of Wild and Endangered Mammals

**Pierre Comizzoli, Nucharin Songsasen, and David E. Wildt**

## Introduction

The forces that are relentlessly pressuring wild animals are well-established and include the loss, fragmentation, pollution, and over-exploitation of habitat as well as emerging diseases, invasive species, and direct human activities, including hunting and urban sprawl. A major contemporary concern also is climate change, which alters how and where animals live. There now are objective data revealing that one in four mammal species and one in eight birds are at high risk of extinction, and one of every three amphibians and half of all tortoises are threatened [1].

Because modern extinctions appear to be occurring at remarkable rate [2], there is growing interest in 'species' and sustaining their viability and genetic integrity [3]. It is well known that a smaller amount of natural habitat almost is always detrimental for wildlife due to reduced food resources and too little space for dispersal of offspring or to find an unrelated mate. One consequence can be incestuous mating that homogenize the genome, causing the expression of deleterious alleles – also known as inbreeding depression. The impact of increasing homozygosity was first demonstrated in ex situ collections 30 years ago [4] when poorly managed, zoo-held animals allowed to breed with relatives were found to experience high rates of neonatal and juvenile mortality. Subsequent ex situ and in situ studies have repeatedly demonstrated the insidious influences of increasing homozygosity, especially on reproductive fitness. For example, our laboratory has documented an increased incidence of cryptorchidism, pleiomorphic spermatozoa, and compromised fertilization in populations or species lacking genetic variation (e.g., African and Asian lion, Florida panther, black-footed ferret [5, 6]). The adverse impacts of decreasing gene diversity extend to other biological systems, including contributing to cardiac anomalies, compromised immune-suppression, and increasing vulnerability to environmental changes (climate and pathogens) [7, 8].

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The gold standard strategy for preserving genetic variation and, thus, reproductive fitness in species has been retaining and protecting massive amounts of habitat. However, this approach becomes unrealistic in a modern world with unfettered, sprawling numbers of people demanding resources that make it impossible to preserve enough wild space to ensure self-sustaining, healthy populations of every species. Carnivores are especially susceptible to loss in space and inbreeding depression [8]. This awareness that saving habitat alone is insufficient has stimulated a groundswell of support for more species studies, including establishing ex situ security populations, especially those at high risk. These intensively managed animals serve as 'insurance' for wild counterparts, but also as an important source of biological (research) information impossible to collect under harsh, uncontrolled field situations. Ex situ operations are expensive, complex, and oriented toward ensuring the retention of all existing gene diversity for at least the next century to ensure species integrity [9]. Maintaining this robustness always is complicated by too few specimens that generally display stressful, self-destructive, and/or dangerous behaviors. Even so, these types of investigations are well worth the risk because there is almost nonexistent biological knowledge (even of the most general sort) for most of the world's 55,000 vertebrate species [3]. In most cases, resulting data have direct (or indirect) application to improving the management and conservation breeding of rare species.

## Value of Reproductive Studies and Fertility Preservation for Rare and Wild Species

Because reproduction is fundamental to species survival, understanding reproductive mechanisms is a high priority. It is well established that there are enormous differences in the specifics of how each species reproduces, even those in the same phylogenetic clade (i.e., family [10, 3]). Over the last 3 decades, our laboratory has studied more than 50 species, and we have concluded that there are as many mechanistic variations in reproduction as there are species [3]. This lack of data on how any given animal reproduces means that there is a need to characterize and describe common sexual patterns (including on the basis of breeding season, behavior, and endocrinology) for thousands of species. For example, a popular tactic in the field or in zoos is 'behavioral endocrinology' where investigators relate animal behaviors to hormonal patterns (gonadal/adrenal) using noninvasive fecal or urinary hormone metabolite monitoring, thereby avoiding animal disturbance [11]. When established, this fundamental scientific information fills a hole in the scholarly database on reproductive life history norms for individual species. It also serves as a source of voucher data that can be predictive of the normal (or abnormal) conditions of a species, population or even individual living in nature or in an ex situ security population. For example, having solid information on the normal breeding season, sexual behavior, and litter size for any given species can assist wildlife managers who may suspect abnormalities in contemporary populations under threat and then can undertake 'adaptive' management. Such information also is critical for risk assessment specialists whose task is to use sophisticated computer programs (e.g., VORTEX [12]), to calculate population status and then undertake research and mitigation priorities. Accuracy depends on knowing the reproductive norms for the target species. Finally, basic and species-specific reproductive data are essential for two types of reproductive management, the first being adapting human- and livestock-related assisted reproductive technologies to developing alternatives to natural mating for retaining all gene diversity [13]. The second involves 'recovery,' situations where a species has become severely threatened, reduced in population size, and it has become essential that every animal reproduce to protect all gene diversity. Both of these management tactics are largely focused on creating self-sustaining security populations in captivity, although recovery programs can eventually include reintroduction and release of animals back to the wild. There are a few models of success, especially using artificial insemination (AI), which allows transporting semen between breeding locations (without the need for moving stress-vulnerable, wild individuals) and overcoming the common problem of sexual incompatibility between computer-selected mates. Examples have been recently reviewed and include the giant panda [14], black-footed ferret [5] (see Fig. 7.1), and scimitar-horned oryx ([15] see Fig. 7.1), the latter two species being returned to the wild after intensive management that includes AI. Embryo-related technologies

**Fig. 7.1** Wild species that are intensively managed ex situ by the Smithsonian's National Zoological Park and partners: **1** black-footed ferret (*Mustela nigripes*), **2** cheetah (*Acinonyx jubatus*), **3** Eld's deer (*Cervus eldii thamin*), **4** scimitar-horned oryx (*Oryx dammah*), **5** tufted deer (*Elaphodus cephalophus*), and **6** Przewalski horse (*Equus ferus przewalskii*). Ovarian tissue samples from these species have been cryopreserved and are currently stored in the Genome Resource Bank at the Conservation Biology Institute

are not used currently for wildlife genetic management because of sorely lacking information on cross-species embryology [16]. There also is an issue of source of recipients for embryos produced from wildlife species, as inter-species embryo transfer is not viable [17]. Nonetheless, embryos have been produced from wild animals, often using in vitro oocyte maturation (IVM) and fertilization (IVF) and occasional offspring produced (see below [16]).

Reproductive biologists studying wildlife benefit from advances in the human infertility and livestock production fields. However, the overall goals of these programs are substantially different – overcoming infertility (humans) versus more efficient/higher quality food production (livestock) versus retention of all gene diversity (wildlife). Nonetheless, these three groups share aligned interests in 'ensuring reproductive health and preserving fertility.' The emergence of the oncofertility field (which explores new approaches for preserving reproductive potential of cancer patients who may lose fertility due to chemical or radiation treatment) has intriguing applications for endangered species enthusiasts charged with conserving genetic variation. For example, there is strong interest in extending the reproductive longevity of a valuable wild animal indefinitely into the future, with the occasional re-infusion of its genes into the contemporary population. Such an approach contributes by avoiding (or mitigating) genetic drift and the tendency for inbreeding in small populations. In this same context, there has been significant effort to articulate the value of 'genome resource banks,' which are organized repositories of biomaterials to be stored and used for managing both heterozygosity and conducting basic and applied research [8]. For wildlife, there are other reasons to extend fertility potential, largely for animals that have not yet produced sufficient numbers of descendants to ensure the passing on of their genes. The specific targets include individuals that (1) are living but fail to natural reproduce, (2) unexpectedly die, (3) are nearing reproductive senescence, or (4) have been long-dead, but there is value in rescuing and re-infusing their genome into the modern population.

## Value of Animal Models for Preserving and Extending Fertility in Wild Species

Some challenges related to understanding and protecting species biodiversity rival the concerns associated to the accessibility to biomaterials faced in field of human reproductive health. More than 20 years ago, we advocated the need for animal models to more efficiently develop assisted reproductive technologies for wildlife [18]. Due to the few numbers of individuals available within an endangered species, it is prudent (and safer) to first test approaches in a common species before applying to the rare counterpart. This philosophy actually emerged because of early failures to directly apply cattle AI techniques to the cheetah (i.e., the epiphany that a 'cheetah is not a cow' concept [10]). This led to the realization that little good information was available on the basic reproductive physiology of any of the existing 37 species of felids, which, in turn, resulted in our developing the domestic cat as a model system. This, in turn, has permitted making many fascinating discoveries on species-specific reproductive mechanisms, for example, a high rate of spontaneous ovulation in the clouded leopard (most felids are induced ovulators), resistance to exogenous gonadotropins in the ocelot, peculiar, protracted luteal function in the Iberian lynx, the ability of female cheetahs to mutually suppress their reproductive cycles, among other phenomena (see reviews [5, 13]). Such findings were the genesis for our encouraging the need for more species-specific research [3]. This point also is relevant if fertility preservation tools developed for humans are to have application to wildlife because it will likely be essential to conduct initial studies in an appropriate (usually taxonomically related) model. Besides the domestic cat as a target (for felids), other valuable models will include the domestic dog (for wild canids), red or white-tailed deer (for wild cervids), brushtail possum (for rare marsupials), or common frog (for near-extinct amphibians). However, there are many animals so specialized that there are no experimental species, for example, the two species of elephants, the five species of rhinoceroses, the giant panda, and killer whale (among hundreds of others). Such cases likely will require more bold and straightforward actions directly to the target species, which is supportable if adequate fundamental reproductive knowledge is available [17].

It also is worth noting that some wildlife species could be interesting natural models for various human reproductive conditions. Such opportunities have recently been addressed and have ranged from the felids (for the ovarian tunica albuginea or for germinal vesicle characteristics [19, 3]) to elephants (for uterine pathologies in aging females, stress-related infertility in a social group, and impact of obesity on reproductive function [3]). Most of these managed animal populations are comprised of many individuals of exact known genetic provenance and variation, an advantage for providing new insights into the role of the individual effect. For example, one could examine an individual component in a reproductive response to a gonadotropin treatment, oocyte quality, or gamete sensitivity to cooling, freezing, or thawing.

## Ways by Which Oocyte and Embryo Culture in Domestic Animals and Humans Can Help Preserve and Extend Fertility in Females of Wild Species

The first order priority for any fertility preservation approach is the capacity for successful in vitro culture of gametes or embryos. It is both technically and logistically possible to harvest follicular oocytes from selected wild female donors by (1) transvaginal or transabdominal laparoscopic recovery or (2) directly from the ovaries after ovariectomy or death [20]. In both instances, this approach requires in vitro maturation (IVM), which is known to produce less developmentally competent oocytes than counterparts matured in vivo [21]. However, the collection of in vivo matured eggs is highly challenging because of the need to (1) develop the appropriate protocols to stimulate folliculogenesis with exogenous hormones and (2) identify the optimum time for collecting oocytes from preovulatory follicles.

Thus, in pragmatic terms, it is more reasonable to rely on recovering immature oocytes from antral follicles, a strategy that can be applied to prepubertal, pregnant or even dead specimens (‘gamete rescue’). For some domesticated mammals and humans, there have been common findings relative to oocyte IVM that likely will be relevant to wild animal applications. For example, it now is well established that the initial quality of the immature oocyte influences subsequent embryo developmental competence in vitro and after embryo transfer [22, 23]. Strict selection criteria are useful for ensuring future developmental success. For instance, some of the oocyte’s morphological traits (i.e., color and cytoplasm homogeneity and number of cumulus cell layers [24]) are important predictors for developmental competence and, more recently, follicle size [25], oocyte metabolism [26], and metabolomics [27]. These same tools are readily adaptable to effectively evaluate oocyte quality in wildlife species.

For genetic management programs involving endangered species, we would expect that IVM followed by IVF will be particularly useful for addressing issues related to aging. For example, cheetahs held in ex situ collections are well known for low reproduction success, which has resulted in many older, genetically important females in the population that still need to pass along their genes to the next generation [28]. Are there human-related fertility preservation tactics that could be useful to rescuing the maternal genome of older individuals? It is clear that oocytes isolated from aged mice and human donors are compromised in ability to complete meiotic maturation and support embryo development [29]. Furthermore, oocytes from older mice and women are developmentally sensitive to mitochondrial damage and exhibit a high incidence of aneuploidy [30]. There are perhaps alternatives to dealing with complete and ‘whole’ old oocytes, for example, focusing on the germinal vesicle (GV) as the target for rescuing valuable genetic materials. It now is known that the GV transferred into an enucleated counterpart oocyte can allow reconstituting a whole oocyte that (following electrofusion and culture) supports normal meiosis [31, 32]. This could also increase the source of ‘rescued’ maternal genomes from genetically valuable individuals that die in ex situ collection or even in nature. Additionally, we recently have demonstrated that there are diffusible factors produced by cumulus-enclosed oocytes that appear especially valuable in oocyte salvage. For example, we have observed in the cat model that the detrimental effects of too few or absent cumulus cells can be overcome to ensure that such non-ideal oocytes can fully mature, fertilize, and develop in vitro [33].

Interestingly, there are unique challenges to IVM/IVF for many wildlife species given the high prevalence of reproductive seasonality. Oocytes collected during the quiescent season(s) of the year are likely to be resistant to conventional developmental culture, with evidence already observed in the red deer [34] and domestic cat [35]. The result generally is low, or non-existent, embryo production during most of the year. However, there is recent evidence that seasonal impositions on oocyte quality can be circumvented by in vitro culture modifications. For example, in our cat model, we have found that supplementing IVM medium with anti-oxidants and increased exogenous gonadotropin concentrations overcomes this seasonal compromise and enhances embryo production efficiency throughout the year [35].

These ideas and practices are emerging from the substantial advances being made in the human fertility field that, in turn, is being driven by vast resources. One of the major underpinnings of all human IVF was the original development of a reliable culture medium for IVF of hamster oocytes, which then was applied to human gametes in the laboratory [36]. Human IVF technology then has progressed extremely fast to a point where new techniques that have enormous potential have not yet been applied to wild animals (such as morphological selection of sperm before intra-cytoplasmic injection, IMSI [37]). Despite the significant use of oocyte- and embryo-related technologies for enhancing reproduction in humans, livestock, and laboratory animals, IVF and embryo transfer have so far had a negligible impact on the genetic management of wildlife species [17]. In fact, there is an amazing lack of research attention on oocytes and embryos even for investigators who specialized in these non-traditional species. We recently surveyed more than 10 years of publications for ten major scientific journals, and, of the 1,330 reproductive papers generated on wildlife, only 19.3% were oriented to oocytes or embryos (compared to 31.3 and 21.3% for sperm and endocrine investigations, respectively; Songsasen, unpublished data). Finally, although there have been a few milestone births, including in the baboon, rhesus macaque, marmoset, gorilla, Indian desert cat, ocelot, tiger, African wild cat, Armenian red sheep, water buffalo, gaur, red deer, llama, and caracal (for a review, see [16]), these are mere hints of the potential of embryo technologies for protecting and preserving wild biodiversity.

## Oncofertility Preservation Approaches that Have Special, Potential Value for Wildlife

Currently, there are four strategies being intensively investigated in the oncofertility field that are particularly attractive for helping achieve wildlife management goals.

### *Ovarian Tissue Cryopreservation*

The ovarian cortex contains thousands of follicles at different developmental stages [38] that are recoverable from individuals at the time of ovariectomy. Of course, a major goal in oncofertility is to develop reliable methods for preserving this source of the maternal genome from women or girls that may lose the capacity to produce viable oocytes after therapeutic treatments. Whole tissue cryo-concepts are highly relevant to preserving fertility potential in wildlife as well (including from adult or prepubertal individuals that might die unexpectedly). We have incorporated this practice into our routine zoological management program at the Smithsonian Institution and with other institutional partners. In this way, the oncofertility consortium and networking process is a model for wildlife operations because excellent communication and interdisciplinary cooperation are critical. In our case, this typically involves close collaboration with curators and veterinarians who expeditiously provide information about a death or medical emergency and then cooperate in excising fresh ovarian tissue that is provided to the laboratory. Research staff then cut ovarian tissue into sufficiently small pieces to allow cryoprotectant permeation and cryopreservation. Others have demonstrated high survival of ovarian tissue (on the basis of cell integrity and grafting success) from most species studied to date [39, 40]. Our laboratory recently demonstrated the value of vitrification over slow cooling for preserving ovarian cortex and primordial follicles from prepubertal and adult cats [41]. Optimal techniques now are being used to routinely bank ovarian tissue samples from a host of rare species, including the black-footed ferret, cheetah, Eld's deer, scimitar-horned oryx, tufted deer, and Przewalski horse among others (see Fig. 7.1). Early results have been quite encouraging, revealing that ~80% of these preantral follicles survive vitrification based on histological integrity, viability staining, and proliferation index (see Fig. 7.2).

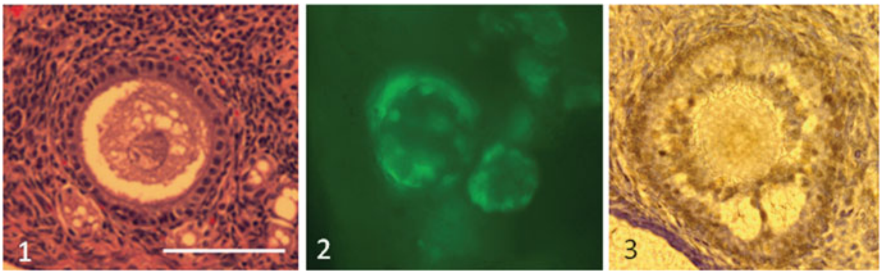

**Fig. 7.2** Assessment of **1** histological structure (eosine/hematoxylin staining), **2** cell viability (calcein-AM staining), and **3** cell proliferation (PCNA immune-staining) in follicles after vitrification of ovarian cortex in felids. For the three pictures, bar = 50 μm

## *Ovarian Tissue Grafting*

The success of transplanting human ovarian tissue to produce viable oocytes (with the now subsequent birth of multiple babies [42]) offers excitement and strong incentive for similar studies in rare wildlife species. Ovarian tissue grafting also has been studied in the mouse [40], cat [43], dog [44], pig [45], sheep [46], rhesus monkey [47], wombat, and wallaby [39]. In all cases, it has been possible to obtain normal-appearing antral follicles from grafted tissues placed in immune-deficient mice. When inseminated in vitro, recovered oocytes from such 'foreign' follicles have the capacity to fertilize and form viable-appearing embryos. And occasionally living offspring have been produced after transfer – in the mouse, sheep, and macaque monkey – from oocytes derived from transplanted ovarian tissue [46, 47, 40]. The benefits of such ovarian tissue xenografting would be similar to those of testis tissue transplantations, specifically in species that take several years to attain sexual maturity like elephants [17]. Again, a major target of interest would be the rescue of the genome of rare, genetically valuable individuals (in combination with the cryopreservation and storage of ovarian tissues). There also is enormous potential for generating new insights into (1) the significance of naturally diverse oocyte morphotypes and mammalian follicular dynamics, (2) responsiveness to exogenous gonadotropins, and (3) the ability to achieve nuclear maturation and fertilization in varied culture conditions.

## *Follicle In Vitro Culture*

The abundance of primordial follicles within the ovary is a significant resource for fertility preservation [48]. A capacity to culture these follicles in vitro to the point of recovering viable oocytes that can achieve nuclear maturation and then fertilize offers enormous opportunities for maternal genome conservation (in association with cryo-banking of gonadal tissues). This approach has been used in the laboratory mouse to produce offspring from cultured primordial follicles derived from both fresh and thawed ovarian tissue [49]. Advances also are gradually being made in both rodent and non-rodent species using isolated preantral follicles. Particularly inspiring have been studies in humans [50] where secondary follicles were able to grow, maintain architecture, and produce steroids in vitro for 15–30 days. The challenges for developing the follicle culture strategy are mostly technical and information-based, but laborious, including (1) matching culture medium and environment to physiological needs of each species, aligning as closely as possible to conditions in vivo; (2) maintaining cell-to-cell communication and signaling; and (3) understanding the influence of epigenetics and the genetic and fertility status of in vitro-derived mature oocytes. It may well be that larger-sized animals (like in the human) will require a long (2 or 3 months) and multi-stage process, whereby primordial follicle growth is initiated in situ by culturing ovarian cortex fragments, and then pre-antral follicles are isolated and grown to advanced stages before steroidogenic function is elicited in somatic cells. The final stage in this complex would be oocyte recovery followed by IVM/IVF and then embryo transfer. To our knowledge, early stage follicular culture has been attempted in only a few non-laboratory species (i.e., sheep, goat, and cattle [51, 52, 53]. Recently, our laboratory has had encouraging preliminary results by adapting ‘mouse methods’ to early stage, preantral domestic dog and cat follicles (in collaboration with Dr. Teresa Woodruff’s laboratory). Over the course of a 10-day culture, follicle size routinely increased by 1.5- to 2-fold (see Fig. 7.3).

## *Oocyte Preservation*

There has been extensive progress in both fundamental knowledge and practical application of cryopreserving mammalian oocytes [54]. Although the cooling, freezing, and thawing of an ovum is much more challenging than the spermatozoon

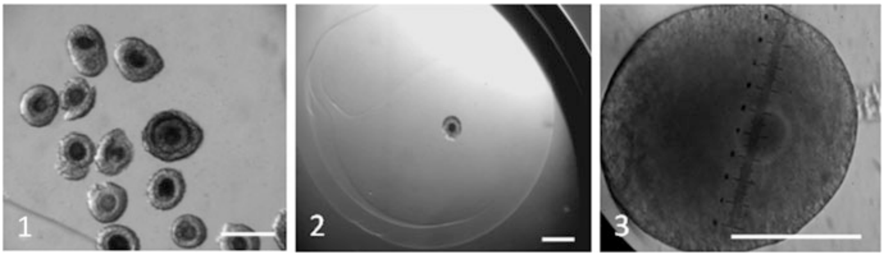

**Fig. 7.3** Domestic dog preantral follicles and enclosed oocytes **1** before culture, **2** after encapsulation in alginate, and **3** after 8 days of in vitro culture. Bars = 200 μm

or embryo, oocytes have been consistently cold-stored and used to produce offspring in several species, with most success in mouse and human [54]. Furthermore, while conventional slow-cooling has been extensively used, both mature and immature oocytes have been cryopreserved recently using ultra-rapid protocols, such as vitrification on electron microscope grids and cryo-loops [55]. Importantly, immature oocytes appear to be more resistant to cryo-damage than mature counterparts because cells at the germinal vesicle stage do not contain a temperature-sensitive meiotic spindle [56]. This characteristic to withstand the stress of extremely low temperature is a significant reason to center more attention on the storage of immature oocytes. But, as with other approaches, there have been few comparative cryo-studies in wildlife species, largely due to the lack of access to good quality oocytes [57]. Regardless, progress for wildlife continues to be linked with parallel studies of taxonomically related domestic animal models and humans [58]. Certainly, continued advancements with the common cow, sheep, goat, cat, dog, and white-tailed deer would have relevance to more rapid progress with wild bovids, small ruminants, felids, canids, and cervids, respectively. It also would be prudent to explore novel approaches for oocyte/maternal genome storage. For example, desiccation has been successful for spermatozoa [59] and could be adapted for the oocyte's germinal vesicle, thereby allowing the stockpiling of female genomes at room temperature.

## Conclusion and Prospects

Fertility preservation strategies used to ensure human reproductive health, including in the field of oncofertility, have significant secondary advantages for conserving biodiversity. This is especially important because there is a growing portfolio of species management and recovery stories benefiting from assisted reproductive technologies and because the highest priority in conservation breeding is to retain gene diversity. Fertility preservation approaches that are in place (or in development) for humans in fact already are protecting the maternal genome of individuals. Thus, there is compatibility and common purpose to these widely diverse targets (humans and wildlife). We can envision laboratories devoted exclusively to the organized collection, culture, storage, and use of ovarian biomaterials from rare species. Furthermore, we foresee the staff of these facilities exploiting the methods developed by colleagues who are working to ensure fertility in human patients. Perhaps there could be direct collaborations with mutual benefits. We also argue that human reproductive specialists could well take advantage of new fundamental knowledge on biological insights from studies of far-from-traditional animal species.

The major limiting factors for advancing fertility preservation in diverse animals will continue to be the significant variance among even closely related species in specific reproductive mechanisms. This will extend to uniqueness in ability to survive cryopreservation and culture of tissues, follicles, and oocytes as well as dealing with the many complexities related to IVF, selecting/managing recipients, and conducting embryo transfer. However, this should not prevent us from exploring innovative approaches such as desiccation and storage of female gametes at room temperature (which also could benefit numerous non-mammalian species, such as birds and fishes).

Important, near-term priorities are clear, starting with more studies on readily available and probably domesticated species that can serve as appropriate models for wild counterparts. There also is a strong need to gain access to rare specimens that die or present opportunities for ovarian recovery during medical procedures in zoological collections or in the field. Finally, it seems wise to promote more interaction among stakeholders in all areas – whether human, livestock, laboratory animal, or wildlife-oriented. For example, there could be significant benefits from the establishment of a fertility preservation network, with benefits ranging from active communication for sharing critical (or simply interesting) information to opportunities for direct collaboration.

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# Part II
# Historical and Legal Perspectives

# Chapter 8
# Placing the History of Oncofertility

**Sarah Rodriguez**

On Fertile Hope's website, Cathy, who at 35 was diagnosed with cervical cancer, shared her feelings and thoughts about her double diagnosis of cancer and infertility. At the time of her cancer diagnosis, Cathy had been married for 3 years and she and her husband had been trying to conceive for 2 years. Following their first attempt using Clomid and insemination, Cathy got pregnant with twins. Their joy abruptly ended, however, when 4 months into her pregnancy Cathy learned she had cervical cancer; her oncologist recommended an immediate hysterectomy. It was, she recalled a year later, "a total nightmare." Cathy and her husband lost the twins and the radiation therapy that followed destroyed her ovaries, putting her into early menopause. After her hysterectomy but before her radiation treatment, her gynecological oncologist asked Cathy if she wanted to harvest some of her eggs. When Cathy said yes, the couple underwent one in vitro fertilization (IVF) cycle before the radiation treatment began. That cycle resulted in six eggs which were fertilized, out of which four embryos were frozen for future use with a gestational carrier. Cathy told Fertile Hope that the whole experience had been devastating:

> Not only did we try to get pregnant for 2 years, then lose twin babies, but I have lost my fertility permanently, and completely. I am in menopause as well. I feel like every last shred of my womanhood has been destroyed. To know that I'll never give birth, never be brought my baby in my arms as I lay happy and exhausted in a hospital bed, is a source of great pain... It is such an isolating feeling. I feel like I'll never be the same as other women. I don't see how life will ever be the same after this tragedy.

When asked by Fertile Hope what her one piece of advice would be to another cancer patient facing possible loss of fertility, Cathy said she would recommend doing "everything you can to preserve your fertility while you can," and stressed the importance of "speaking to a fertility specialist before you do anything that will permanently damage your ability to have children [1]."

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As Cathy's story illustrates, cancer and infertility as a result of treatment are not defined solely by a medical diagnosis; they are also painful personal experiences occurring within a larger social and cultural context. I open with Cathy because in her narrative we find the medical, cultural, and personal – a microcosm of the emerging field of oncofertility. Her story, like the story of oncofertility, exists now because of a convergence of many medical and non-medical factors, including, but not limited to, the following: changes in cancer research, diagnostics, and treatment; an increase in the number of younger people, and people like Cathy of child-bearing age, being diagnosed with, and surviving, cancer; a wider cultural acceptance of cancer as a publicly discussed and personally acknowledged disease; the infusion of public and private dollars into cancer as well as fertility/infertility research; recent developments in medical knowledge about fertility/infertility treatments; and a growing cultural acceptance of the use of assisted reproductive technologies (ART) like IVF. Additionally, Cathy's story and the story of oncofertility are part of the contested medical and cultural discussion on reproductive decision-making and the status of the fetus and embryo that has emerged in this country over the past several decades. The stories also reflect the transformations in medical and cultural understandings about pregnancy, birth, and fertility; changes in ideas about motherhood and the cultural importance of motherhood as well as the social role of women and what it means to "be" a woman; shifts in the dynamic of the doctor-patient relationship; and the consumer culture of both medicine, where some have health care and some do not, and babies, where some are able to afford fertility options while others are not. These ideas and events are among those which cumulatively brought forth oncofertility, and they will continue to overlap and influence each other as the field emerges. I will briefly draw out a few of these factors through Cathy's story, and by doing so will begin to present a picture for future work to contextualize the history of oncofertility.

Cathy's story could not have been told in 1909 or 1959. Indeed, in both of these eras, Cathy's physician may not have uttered the "C-word" to her. William Halstead, originator of the Halstead mastectomy and medical doctor who practiced in the early twentieth century, rarely told his patient she had cancer, though he did often tell her husband [2]. In the 1950s, physicians used words like tumor or growth to avoid using the "C-word" with their patients because it was seen as a stigmatizing disease [3, 4]. There is some question of how far to take the idea that patients suffered in silence for a majority of the twentieth century because of the social stigma of cancer. Historian Barbara Clow persuasively argues that "neither private nor public discourse entirely supports" the assumption that Americans were as reticent to talk about cancer as the term "silence" implies. Regardless, a patient's options for preserving her fertility before cancer treatment or treating her infertility after, even assuming that topic would have been discussed as part of her cancer therapy, would have been far fewer in the not-so-distant past [5, pp. 297–298].

However, this does not mean a woman in 1909 or 1959 would have been without options for medically treating her infertility. While doctors probably did not make a connection between cancer treatment and resultant infertility in 1909 – more on cancer treatment in a moment – if a patient had gone to her gynecologist because of her inability to conceive, there is a possibility that he (and I use the pronoun here on purpose) may have discussed infertility treatment options with her. Physicians, particularly gynecologists, first published their accounts of treating infertility in the mid-nineteenth century, just as gynecologists sought to establish themselves as specialists. As early as 1856, J. Marian Sims started to treat infertility surgically, specifically incising the cervix to make the opening to the uterus wider. And though he never did so as a first response to infertility, Sims also experimented with artificial insemination with the patient's husband's sperm, though at least one of his peers used donor sperm if the husband's proved lacking [6].

In the seventeenth century, Americans would not have considered seeking medical attention for their inability to conceive; doing so may have been viewed as defying the Lord. But by the late nineteenth century, while women probably did still pray, they also increasingly turned to doctors to help them conceive. By that time many more physicians had joined Sims in operating to restore fertility. Margaret Marsh and Wanda Ronner, in their history of infertility in the United States, found that by the late nineteenth century, and increasingly so by the early twentieth, before annual visits to the gynecologist became commonplace, women from both working-class and middle-class backgrounds, regardless of race, sought infertility treatments from doctors. Women with less means went to clinics where they were often treated for free or reduced costs. Though we do not know the rate of success for these treatments, by going to the doctor seeking assistance for their inability to conceive, women from the middle as well as the working class were indicating that they considered infertility a medically treatable condition by the early twentieth century [6].

By the late nineteenth century and through most of the twentieth century, the medical options available to women included surgery to unblock fallopian tubes, artificial insemination with a husband (or donor's) semen, and "ovarian transplantation" which involved grafting portions of an ovary from a fertile woman into a woman who lost her ovaries from disease. Options in ART increased during the twentieth century. Though John Rock and Miriam Menkin in the 1940s fertilized four human eggs in vitro, and the publication of their achievement fanned the hopes of many women having difficulty conceiving, the first baby born from this technology did not arrive until the late 1970s [6]. By the 1980s, the ART initially chosen by Cathy, IVF, ceased to be experimental; indeed, it had become part of the accepted reproduction landscape. As Lisa Hope Harris described in her history of IVF, cultural conceptions of motherhood, of the family, and of working women shaped IVF, and the technology in turn reshaped social ideas about motherhood, the family, and working women. Twenty years after IVF technology brought forth the first "take-home" babies in the late 1970s and early 1980s, the technology was no longer seen just as a panacea for those unable to conceive. More importantly for its further development, according to Harris, was how the media showed it as a break-through for women who delayed childbirth because they had entered the professional workforce. IVF helped reshape the public's discussion about women's pregnancy options: IVF was not simply a response to women delaying pregnancy, it also enabled women to feel like they could delay pregnancy, argued Harris. Or at least that was how mainstream media represented this technology. IVF and other ART became tools for women (and couples) with the means to pay for them – whether or not they were the ones most in need of such technologies. Harris's account of the history of IVF in the United States reveals the cultural and economic influences on the development of medical technology [7].

Part of the cultural landscape from which IVF blossomed was the very vocal political element uncomfortable with assisted conception and the status of embryos created through medical intervention. In the late 1960s, when assisted reproduction techniques like IVF were still in their gestational stage, the majority of Americans disapproved of attempts to create life through such means, an early indicator of what became a greatly contested medical and cultural discussion on reproductive decision-making. As Harris described, the aversion, even hostility, some Americans felt toward assisted reproduction and the resultant embryos, meant that technology developed largely outside of public purview: federal lobbying by pro-life groups resulted not only in no public funding of the research but also no federal regulation of that research. As a result, ART developed in the private, market-driven world. During the late 1980s, one doctor compared the lack of IVF regulation to the Wild West, saying "It's kind of like Dodge City before the marshals showed up" [7, p. 311]. IVF remained largely unregulated on a federal level until the passage of The Fertility Clinic Success Rate and Certification Act of 1992, which required all fertility clinics report pregnancy success rates (many of them were advertising enhanced success rates, sometimes deceptively high). At the same time, the Federal Trade Commission began targeting IVF clinics who were padding pregnancy success rates. By the early 1990s, Harris noted, people seeking IVF had access to information about clinics, but these clinics still operated within a marketplace, not a research, environment, and the protections regarding the use of reproductive technologies were largely consumer protections [7]. According to Marsh and Ronner, this left it up to individual clinics and practitioners to decide what technologies and techniques were acceptable, to establish their own guidelines for deciding what successfully treating an infertile couple meant, and to decide whether or not they wanted to follow the practice guidelines of the American Society for Reproductive Medicine. Further, their existence solely within the marketplace also enabled them to establish their own fees based on what the market could bear [6].

Though Cathy speaks decades later, after IVF had become a medically and culturally established technology, her horror of being made infertile because of her cancer treatment touches on the continued importance placed on biological motherhood as a defining characteristic of womanhood. As Cathy told Fertile Hope, "to know that I'll never give birth, never be brought my baby in my arms as I lay happy and exhausted in a hospital bed, is a source of great pain. . . It is such an isolating feeling. I feel like I'll never be the same as other women" [1]. Because of her resultant infertility, Cathy expresses great pain at not being like other, presumably "real" women, women who bear children; indeed, she feels "like every last shred of my womanhood has been destroyed" [1]. Here Cathy ties her feelings of being female directly to her fertility, an identity with long historical roots, though the cultural context – and the cultural stress placed on bearing children – shifts. A married woman in the 1950s, for example, experienced the pain of her infertility during a period of strong social pressures to have a child, compared to the 1970s when cultural worries about overpopulation resulted in less social stress placed on bearing children [6]. Though the individual pain would have presumably been as sharp for each woman, the larger cultural response to her infertility would have been different.

The desire to become a mother is rooted in more than societal or historical pressure; the desire is also personal. Like many women, Cathy viewed motherhood as a future role she would experience, and even though it was a vision of her future self, motherhood was a significant part of how she defined her present self as female and as an adult woman. And like many other young women with cancer, the diagnosis of cancer threatened her life and the possibility, and then reality, of infertility eliminated what she always imagined herself as being: a mother. As Cathy told Fertile Hope, “I don’t see how life will ever be the same after this tragedy” [1]. Motherhood has been perhaps the primary role of women throughout American history [6, 8]. It is this role, a role ethicist Hilde Lindemann Nelson would refer to as a “master narrative,” a story that serves “as summaries of socially shared understandings,” that Cathy desires and feels that cancer has taken from her [9, p. 6]. But it is also what is motivating Cathy and her husband to look for other means to parenthood.

The fact that Cathy and her husband are using a reproductive technology and a gestational carrier to become parents is a reflection of the medicalization of infertility. During the late nineteenth and early twentieth centuries, as physicians increasingly claimed the ability to treat infertility, and women increasingly sought out their services to do so, the inability to become pregnant or maintain a pregnancy changed, as Marsh and Ronner argue, “from a social state into a medical condition” [6, pp. 2–3]. Once infertility became a medical condition, many couples changed from finding parenthood through social means, like assisting others raising their children, to finding parenthood through medical treatment [6].

Cathy and her husband’s desire to use a gestational carrier also reminds us of the fluidity of historical and cultural ideas of the means to motherhood. What and how one becomes a mother, the importance placed on physically bearing a baby, and how pregnancy and motherhood is medically, personally, and popularly seen as a part of being female, is not contextually historically constant. Motherhood, as historians Rima Apple and Janet Golden remind us, is neither “a static concept nor is it a homogeneous category” [10, p. xiii]. In Colonial times, for example, fertility was necessary for familial survival, but infertile (white) couples raised children brought forth in a variety of ways: through taking in motherless children, adopting parentless children, or raising children living with them whose parents sent them to work in their household. Belonging to a household, not just biology, defined membership in a family [11]. Because she is exploring an alternative path to becoming a mother, Cathy is part of these more expansive historical maternal roots.

At 35, Cathy was still of child-bearing age (and actively trying to conceive) when she was diagnosed, reflecting the increase in the number of younger people who are today diagnosed with and survive cancer [12]. Her age, and the fact that beneficial treatment was available to her, illustrates the innovations made in cancer research and treatment that were a direct result of the federal government’s investment in medical research. Beginning in the 1930s with the creation of the National Cancer Institute in Bethesda, Maryland, and then following World War II, the United States government intensified the amount of financial support for cancer research as part of the beginnings of a national medical research policy [13, 14]. Following World War II, the federal government dramatically increased spending on cancer research: in 1947, $14 million went to fund cancer research, growing to $110 million in 1961, then nearly doubling to more than $200 million in 1970 [15]. Since 1971, when President Richard Nixon declared a "war on cancer" and the federal government directed the National Cancer Institute to coordinate research and innovations in the detection, diagnosis, and treatment of cancer, the number of cancer survivors has increased, along with the acceptance that a "C-word" diagnosis did not equal death [12].

Cancer control in the late nineteenth and early twentieth centuries largely revolved around prevention, early detection, and quick intervention.[1] Though some physicians felt looking at the causes of cancer was equally important, by and large, efforts were directed at early detection and treatment. Public education encouraged people to see their doctors as soon as possible if they suspected cancer. In 1913, surgeons founded the American Society for the Control of Cancer to advocate for awareness of early signs of the disease because they believed people came to them too late, having been either unaware of indications of cancer, or unsure of whether the cancer could be cured, or too fearful of what treatment entailed to seek medical attention until the disease had progressed past the point where doctors could effectively treat it [14]. Although radium was beginning to be used to treat cancer in the 1st decade of the twentieth century, treatment largely consisted of surgery until after World War II, when chemotherapy and radiation became part of standard cancer treatment [15, 16]. The stress placed on early detection and treatment dominated cancer control until the 1970s, when greater weight began to again be placed on lifestyle and environmental causes of cancer [14].

The 1970s also saw changes concerning the structure of the doctor–patient relationship. That Cathy discussed her cancer treatment and fertility preservation options with her doctor, and that Cathy recommended anyone else facing cancer treatment and possible infertility "do everything you can to preserve your fertility," illustrates how patients today expect to be able to discuss their health care options with their provider and actively participate in their treatment options. This ability to "take control" of one's options for cancer treatment and fertility preservation, as Cathy recommends, rose out of the patients' rights as well as women's rights movements in the 1970s. But Cathy's stress on being active is also part of a longer

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[1] Both cancer and infertility, as medical conditions, are defined by changes and advancements in theories, research, and treatments; but advances in the medical understanding of infertility or cancer have not themselves initiated increases in demand for treatment. An increase in the use of medical treatments for cancer and ART has more often stemmed from a popular perception that resources existed for the treatment of cancer and infertility – whether or not those resources in fact existed [6, 15]. Changes in the social and cultural understandings of infertility and cancer have played just as prominent a role in their history as changes in medical ones.

history, one where American women, through membership in women's clubs and voluntary associations, participated in cancer awareness programs beginning in the early twentieth century [17, 18]. Moreover, before the 1970s movements, though most patients passively consented to their physicians' recommendations and doctors controlled most of the interaction with their patients – even, as mentioned above, not telling them of their cancer diagnosis – historian Barron Lerner found some patients did take some part in making decisions about their cancer treatment, even challenging their doctors' decisions [3].[2] Additionally, Cathy's desire to discuss her fertility options also points to her historical link with women who in the past negotiated with their doctors about what infertility treatments they would undergo. In their history of infertility in the United States, Marsh and Ronner found that some patients in the late nineteenth century refused certain treatments or demanded treatments other than what their doctor prescribed, reflecting a certain amount of knowledge on their part about available medical options [6].

As I have briefly touched on here through Cathy's story, medical and non-medical factors contributed to the emergence of oncofertility, and these factors will continue to shape this field. Delving deeper into the history of oncofertility will, I suggest, help us be more sensitive to the medical, social, personal, and ethical issues involved today, and will help us better frame the questions about the field's future use.

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[2] See also Leslie J. Reagan's analysis of the way education regarding cancer was largely directed at women during the first half of the twentieth century [18].

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# Chapter 9
# Medical Hope, Legal Pitfalls: Potential Legal Issues in the Emerging Field of Oncofertility

**Gregory Dolin, Dorothy E. Roberts, Lina M. Rodriguez, and Teresa K. Woodruff**

## Introduction

The United States annually spends over $200 billion on cancer treatment and research [1]. Over the past several decades, tremendous progress has been made in combating this disease. The 5-year survival rate for cancer has increased from 35% in 1950–1954 to 67% in 1996–2004. Moreover, over the last 40 years, survival rates for childhood cancer have risen from 20% to 81% [2]. However, the very success of new and improved therapies has created a host of problems that were not previously considered. One of the results of the increased rate of post-cancer survival is the commensurate desire of former cancer patients to return to healthy lives, which for many includes having children. Unfortunately for many, this desire is difficult to fulfill, because the medication that succeeded in battling cancer is also quite often toxic to the reproductive organs. Thus, many people are able to live longer lives, yet they feel that their lives are incomplete because they became infertile. Whereas in the past fertility was not even part of the discussion when deciding on the proper cancer treatment, now it is a top concern of many newly diagnosed cancer patients [3]. In response to this concern, medical researchers are investigating several approaches (many of which are described in this book) to preserve cancer patients' reproductive options.

Like many scientific breakthroughs, especially ones dealing with human reproduction, oncofertility enters an area of legal and ethical uncertainty. As the scientific and medical advances in the field of oncofertility are made, researchers, doctors, and patients need to be aware of hidden legal pitfalls and hazards. In this chapter we will discuss some legal questions that are likely to arise in the field of oncofertility. In discussing these questions, we will apply now-existing legal principles in order to develop a framework for answering these questions.

We begin our discussion by identifying the values at stake in the field of oncofertility. These values include the constitutional protection of the rights of women and minors to bear children and to use reproduction-assisting technologies, as well as

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the feminist critique of gendered expectations that may pressure women to use these technologies.

The medical options already available to patients and those that are being developed are discussed elsewhere in this book, so we will omit the scientific discussion. However, basic understanding of the medico-scientific principles is useful for fuller appreciation of the legal implications.

After laying out the legal groundwork, we will address the potential legal questions that may emerge as the field of oncofertility develops. Can or must parents consent to a "medically unnecessary" surgery on behalf of a child to preserve her fertility? Who owns the excised tissue and the gametes contained within it? Additionally, legal issues that arise in conducting research on excised tissues for the purposes of future reproduction will be discussed. We avoid making definitive predictions of what the law relating to oncofertility *will* look like. Rather, our purpose is to suggest a framework based on the current state of the law which can help to answer these questions.

## What Is at Stake?

### *Is There a Right to Reproduce?*

The right to reproduce is firmly entrenched in American and international law [4, 5]. The United States Supreme Court has declared and reaffirmed the right to bear children in several decisions. For instance, in *Skinner v. Oklahoma* [6], the Court defined this right as "fundamental to the very existence of the [human] race." Subsequent cases involving the right to use contraceptives made clear that substantive due process guarantees the right to reproductive decision-making. In *Griswold v. Connecticut* [7], protecting married couples' right to use contraceptives, the Court described reproductive freedom as "older than the Bill of Rights – older than our political parties, older than our school system. . . and intimate to the degree of being sacred." Similarly, in *Eisenstadt v. Baird* [8], the Court extended this protection to unmarried people, holding that the right to privacy encompasses the "right of the *individual*, married or single, to" make his own decisions as to "whether to bear or beget a child." In a line of cases beginning with *Ohio v. Akron Center for Reproductive Health* [9], the Supreme Court held that minors, no less than adults, possess the right to decide whether to bear a child.

In addition to being firmly embedded in US case law, the right to reproduce is also protected under international law. For instance, the United Nations Universal Declaration of Human Rights proclaims that "[m]en and women of full age . . . have the right to marry and to found a family" [10]. The United Nations International Covenant on Civil and Political Rights states that "[t]he right . . . to found a family shall be recognized" [11].[1] The European Convention on Human Rights also

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[1] The United States is a signatory to this Covenant, and has formally ratified it, though with some reservations. 138 Cong. Rec. S8068–71 (1992).

adheres to this view [12]. The Cairo Declaration on Human Rights in Islam, adopted in response to the Universal Declaration of Human Rights, states that "[t]he family is the foundation of society . . ." [13]. Though coming to differing conclusions on the ultimate issue of the possession of frozen embryos, both the European Court for Human Rights and the Supreme Court of Israel held that a right to "become a parent" is a fundamental human right [14]. In short, the right to have children is a nearly universally acknowledged and honored right.[2]

Some of the fertility-preserving methods employed in the field of oncofertility rely on scientific advances allowing for gametes to develop in vitro, rather than in vivo. These methods raise the question whether in vitro reproduction enjoys the same status as its much-older counterpart. While significant social and moral issues with respect to assisted reproductive technologies ("ART") arise, current case law and state statutes suggest that the constitutional protection of reproductive decision-making extends to individuals' use of these techniques in order to conceive.

Would it be constitutional for a state to ban or severely restrict the use of ART? Although no court rulings explicitly recognize constitutional protection of a right to assisted reproduction, a review of court cases, statutes, and academic literature provides convincing evidence that US law takes for granted that such a right exists. First, many state statutes recognize the legality of ART and support citizens' access to these services. For instance, an Illinois statute that regulated abortion and other procedures on embryos explicitly declared that "[n]othing in th[e statute] is intended to prohibit the performance of in vitro fertilization" [15]. Louisiana has adopted statutes regulating in vitro fertilization ("IVF") [16, 17], and New Hampshire and Pennsylvania have statutes governing the obligations of sperm donors for IVF procedures, thus recognizing (at least implicitly) the right to use these technologies [18, 19]. The federal government also implicitly recognizes the legality of IVF treatments [20]. In addition, "fourteen states currently require some types of health insurance plans to include coverage of certain infertility services or to make such coverage available" [21]. Thus, while no state explicitly protects a right to use IVF, both state and federal government implicitly acknowledge that such a right exists. These statutes also recognize, however, state and federal power to regulate assisted reproduction, and it remains unclear the extent to which the right to procreate limits such regulation.

Second, court cases have similarly acknowledged a right to use ART. Several courts both in the United States and abroad have adjudicated disputes over ownership of fertilized frozen embryos. While the various courts came to differing conclusions, they all took the underlying right to access ART as a given. For instance, in *Davis v. Davis*, Tennessee's highest court implied – without explicitly holding – that the right to procreate by the means of IVF is within the ambit

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[2] To be sure, the right to bear children is not an unfettered one. Some courts have held that the state may limit a person's ability to reproduce in certain circumstances such as imprisonment or flagrant disregard toward child support obligations. See, e.g., Gerber v. Hickman, 291 F.3d 617 (9th Cir. 2002) (en banc) (holding that prison inmates lose their right to reproduce); State v. Oakley, 629 N.W.2d 200 (Wis. 2001) (upholding a condition of probation requiring a "dead beat" to avoid having another child).

of the constitutional right to privacy [22]. The New Jersey Supreme Court adopted the same reasoning in *J.B. v. M.B* [23]. The New York Court of Appeals, while not explicitly endorsing *Davis*, advised parties to IVF to enter into agreements on disposition of zygotes, thus treating ART as a legal means of reproduction and perhaps taking for granted its constitutional protection [24].[3]

At the same time, some courts have placed limits on individuals' right to use ART. In *In re Baby M*, for example, the New Jersey Supreme Court voided as against public policy a surrogacy contract between the Sterns and the birth mother, Mary Beth Whitehead, when she decided to keep the baby [25]. Thus, while the court implicitly acknowledged Mr. Stern's right to use IVF, it held that the constitutional right to reproduce did not encompass state enforcement of surrogacy contracts.[4] Nor have courts held that the right to use ART includes a claim for state assistance to pay for these services. Louisiana and Nevada explicitly exempt health insurance plans from having to cover IVF in statutes that mandate coverage for other reproductive health services, and many states do not provide infertility treatment in their public medical assistance programs [21]. These limits on the right to access ART fit within the current US Supreme Court interpretations of reproductive liberty as a negative right against state interference [4, 21].[5] In other words, while states are free to mandate insurance coverage of ART, the Constitution does not require it.

Although the right to access ART, if one can afford it, is accepted by legislatures and courts, women's use of these technologies remains controversial. On the one hand, some scholars see access to assisted reproduction as extending women's reproductive liberty [5, 26]. Technologies that help women have children enhance the choices they have to fulfill their reproductive desires. In the context of oncofertility, it can also be argued that techniques that restore fertility to female cancer survivors place women on equal footing as men, who are easily able to store semen for future use. Oncofertility can be viewed as a gender equalizer that gives women and girls the same reproductive options as men and boys. On the other hand, feminists have long questioned the gendered forces that lead many women to use ART [27, 28]. They point out that women's desire to bear children is influenced by the stigma of infertility and the expectation that all women will become mothers. Added to this is the desire to have a genetically related child. Some women feel a duty to undergo the expense and physical trauma entailed in IVF, rather than remaining childless or adopting a child, in order to be acceptable to a male partner and the

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[3] See Also *In re* Marriage of Witten, 672 N.W.2d 768 (Iowa 2003); Litowitz v. Litowitz, 48 P.3d 261 (Wash. 2002); A.Z. v. B.Z., 725 N.E.2d 1051 (Mass. 2000).

[4] John Robertson argued that procreative liberty includes a constitutional right to state enforcement of surrogacy agreements [5]. For a critique of Robertson's position, see Roberts DE. Social Justice, Procreative Liberty and the Limits of Liberal Theory: Robertson's Children of Choice. *Law & Soc. Inquiry*. 1995; 20:1005–21.

[5] Two federal appellate courts have rejected the claim that health plans that exclude infertility treatments violate Title VII of the Civil Rights Act of 1964 or the Pregnancy Discrimination Act (Krauel v. Iowa Methodist Med. Cent., 95 F.3d 674 (8th Cir. 1996); Saks v. Franklin Covey Co., 316 F.3d 337 (2d Cir. 2003)) [21].

wider society. Girls whose ovaries have been preserved may feel added pressure to become mothers because of the effort and expense that went into the procedure. Although many believe that access to ART is essential to reproductive freedom, others see it as reinforcing unjust expectations about women's reproductive roles.

This review of statutes and court decisions shows that US law currently acknowledges that procreative liberty encompasses, subject to some degree of state and judicial regulation, the right to use ART. Having established this, we now proceed to the discussion of unsettled legal issues that may affect oncofertility in practice, and thus the treatment options given to patients.

### *What Are the Reproductive Rights of Minors?*

Generally speaking, minors have the same reproductive rights as adults, except that states have greater power to regulate the conduct of minors. In *Bellotti v. Baird*, the Supreme Court held that a requirement of parental *consent* to abortion, without a judicial bypass provision, was unconstitutional. Although the Court subsequently has been more solicitous of legislative attempts to interpose adult involvement in the minor's abortion decisions, it has never allowed any state to legislate a scheme under which a minor's decision could be vetoed by a parent (unless such a "veto" is also sustained by an impartial judge) [29]. Additionally, most states permit minors to use contraceptives without seeking adult permission [30, 31].

With respect to deciding to bear a child (as opposed to deciding to terminate a pregnancy), minors' rights are even broader. The age of consent in many states is well below the age of majority (especially when both participants are minors). No state permits any third party to require a minor to get an abortion should the minor become pregnant. In other words, if a minor decides to bear the child, the decision is hers alone. Finally, as discussed below, parents cannot deprive minors of future reproductive capacity, absent compelling need *and* a court order. In short, a minor's liberty to determine his or her own reproductive future is constitutionally protected from restraint except in narrow circumstances that are subject to judicial review. Minors enjoy the same constitutional protection of their reproductive rights as adults do, even if exercising some of these rights (due to the limitations of biology) is deferred until they mature.

## The Legal and Moral Questions

### *Who Can Consent to a Medical Procedure and What Are the Limits?*

As with any other medical procedure, the patient must freely and voluntarily consent to undergo ovarian tissue cryopreservation in order for the protocol to be legally (and morally) employed [32, 33]. Any medical manipulation of the patient without such consent, under our laws and traditions, constitutes battery (even if medically beneficial to the patient).

Generally speaking, a competent adult can consent to almost any legal medical procedure, including one that will permanently alter his or her reproductive capacities [34–36]. Thus, adults are free to consent to tubal ligation or vasectomies, even though these procedures are most often irreversible, and thus will permanently limit reproductive capacity of the patient. Conversely, as discussed below, competent adults can consent to procedures that will preserve or enhance their reproductive capacities. Thus, when the oncofertility patient is a competent adult, she can legally and ethically decide for herself whether or not she wants to undergo an invasive procedure in hopes of preserving future reproductive capacity.

Consent, while a sine qua non of ethical medical practice, is not the only consideration. The first principle of medicine is "first, do no harm." In other words, the physician ought not perform procedures or prescribe treatment that carries risks, but no identifiable benefits. This does not mean that experimental treatments are out of bounds, but, rather, that prior to asking for the patient's consent, physicians must assure themselves that the treatment offered carries more potential medical benefits than harms.

With respect to minors, the question of consent becomes more complicated. In most circumstances, parents (or legal guardians) are invested with legal authority to make medical decisions for their minor offspring and generally can choose when, whether, and from whom to seek care for their minor children [37].[6] This discretion is given to parents for good reason. As the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research observed:

> [A] family member ought usually to be designated as surrogate to make health care decisions for an incapacitated patient in consultation with the physician and other health care professionals:
>
> (1) The family is generally most concerned about the good of the patient.
> (2) The family will also usually be most knowledgeable about the patient's goals, preferences, and values.
> (3) The family deserves recognition as an important social unit that ought to be treated, within limits, as a responsible decisionmaker in matters that intimately affect its members.
> (4) Especially in a society in which many other traditional forms of community have eroded, participation in a family is often an important dimension of personal fulfillment.
> (5) Since a protected sphere of privacy and autonomy is required for the flourishing of this interpersonal union, institutions and the state should be reluctant to intrude, particularly regarding matters that are personal and on which there is-. [sic] a wide range of opinion in society [38].

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[6] There are exceptions to this rule. Parents cannot refuse life-saving treatments, such as blood transfusions, and may not deprive their children of medical attention when such deprivation is tantamount to child abuse. However, with respect to routine procedures, the choice lies with the parents.

The United States Conference of Catholic Bishops similarly notes that "family members and loved ones" are usually "in a position to know best the patient's wishes" [39]. In addition to these moral and ethical observations, American courts have held that parents have a constitutional right to bring up children as they deem best without interference by the state, absent a compelling state interest to the contrary [40–43].

The parent's right to decide on a child's treatment is not absolute. Unlike a competent adult who can choose to reject any treatment for any or no reason, a parent cannot reject a medically necessary treatment on behalf of his child. Parental decisions regarding medical treatment are limited by the principle that parents must act in the best interest of the child [44–46]. Thus, for instance, a parent may not decline a blood transfusion on behalf of his child, even if both the child and the parent hold religious views that prohibit blood transfusions [47–49]. Similarly, parents cannot consent to enroll a child in clinical research "unless it is intended to promote the health of the population represented by the potential subject, [and] the research cannot instead be performed with competent persons" [50]. Furthermore, parents are limited in their ability to consent even to experimental treatment of the minor by two considerations. "First, if the treatment is not medically necessary for the minor, it must not be unreasonably harmful. Second, the treatment must be to the benefit of the minor, and not just to the benefit of the minor's parents or other family members." [51, 52]. These limitations are not surprising if one keeps in mind the overarching requirement that in deciding on the course of treatment, parents must act in the child's best interest.[7]

In addition to obtaining parental consent, it is often useful to seek the child's input into the treatment decision. First, such input may carry legal weight. Second,

> [s]eeking the assent of a minor who is not legally authorized to consent demonstrates respect for the decision-making skills of a nonautonomous individual to the extent that he or she is able to participate in the decision. This is particularly relevant for adolescents who are cognitively mature but below the age of legal majority and still dependent upon adults for their basic health care decisions [53, 54].

Third, seeking minor's assent may be a prerequisite to administering the treatment effectively because it ensures that the patient is compliant.

Thus, when dealing with pediatric patients the simple formula of "'efficacy of treatment' plus 'patient's consent' equals 'administering the treatment'" does not hold. In pediatric cases, in addition to assuring themselves of the treatment's benefits, physicians must also make sure that they seek parental consent and the child's assent (where practicable). These considerations ultimately are subject to a judicial determination of the best interests of the child.

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[7] When there is room for a legitimate difference of opinion as to which treatment is best, the state defers to the parental choice. Parents are, however, precluded from choosing a treatment that has no identifiable benefits to the minor [37].

## *Are There Limitations to Proxy Consent in the Reproductive Context?*

As the above discussion demonstrates, although parents are generally permitted to make medical decisions for their minor children, these decisions must be in the best interests of the child. In the area of sexual health and reproduction, parents' decisional rights are further limited. For instance, courts have held on numerous occasions that parents cannot veto a minor's decision to seek an abortion. Numerous states have also enacted legislation that allows a minor to seek treatment (or preventative measures) for pregnancy and sexually transmitted disease without parental involvement or consent. There are weighty reasons why reproductive decisions are excluded from otherwise nearly plenary parental authority to make medical decisions on behalf of their offspring. First, because decisions that affect the reproductive capacities of minors necessarily interfere with "one of the basic civil rights of man," they must be heavily scrutinized and sometimes disregarded. Second, it may be more likely that parental involvement in a minor's decisions on such sensitive issues as sexual activity and pregnancy will not serve a minor's best interest.

In exploring the limits of parental authority over reproductive and sexual health decisions of minors, it is useful to look at the jurisprudence governing four procedures – male circumcision, female genital cutting, sex assignment surgery, and sterilization. All four are elective procedures,[8] but all are not treated in the same way by the legal system [55]. Looking at the differences in the leeway permitted to parents in each of those circumstances, and the underlying reasons for those differences, can help in constructing a framework within which questions about the legal treatment of oncofertility can be answered.

### Male Circumcision

Male circumcision involves removal of the foreskin of the penis. It is a procedure usually performed on a newborn child, sometimes for religious or cultural reasons. Following World War II, the practice of circumcision became quite common in the United States. Parents routinely consent to the procedure and it is routinely performed. Lately, however, the practice started drawing criticism as being incompatible with the child's right to bodily integrity and autonomy [56, 57]. In 1999, the American Academy of Pediatrics issued its position statement on circumcision, recommending that doctors should not routinely advise parents to seek circumcision of their sons, but should, at the same time, yield to parental request for the surgery [58]. Despite the increased criticism, male circumcision remains legal.

For instance, in a 2008 case involving a dispute between divorced parents over the decision to circumcise a minor male child, the Oregon Supreme Court held that the

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[8] In some cases, male circumcision may be medically necessary, but those constitute a minority of all circumcisions performed in this country.

custodial parent has legal authority "to make medical decisions for his or her child, *including decisions involving elective procedures* and decisions that may involve medical risks" [59]. The court explicitly noted that "although circumcision is an invasive medical procedure that results in permanent physical alteration of a body part and has attendant medical risks, the decision to have a male child circumcised for medical or religious reasons is one that is commonly and historically made by parents in the United States." The court did limit parental authority somewhat by directing the trial court to examine the views of the minor (12-years-old at the time) and take them into account.

In *State v. Baxter* [60], the Washington Court of Appeals noted that "ritual circumcisions . . .have been performed for thousands of years and have *never been held contrary to public policy*." Courts in other states, in addressing various claims of medical malpractice and improper informed consent for the circumcision procedure, have uniformly assumed that a properly performed circumcision after a proper informed consent by one of the parents is fully consistent with the law [61–63].

## Female Genital Cutting

By contrast, consider a procedure performed on minor females commonly referred to as "female circumcision" or "female genital cutting," which involves "partial or total removal of the external female genitalia or other injury to the female genital organs *for non-medical reasons"* [64]. Like male circumcision it may be performed for religious or cultural reasons, and like male circumcision it is "an ancient cultural or social custom" [65]. Unlike male circumcision, however, female genital cutting is universally viewed (in the American legal system) as a procedure to which parents cannot legally consent.

For instance, in 1996, Congress passed the Criminalization of Female Genital Mutilation Act, which makes it a crime to perform the procedure on a minor.[9] In enacting the statute, Congress found that "the practice of female genital mutilation often results in the occurrence of physical and psychological health effects that harm the women involved." This finding is supported by a similar statement of the World Health Organization. A number of states have enacted similar prohibitions of the practice.[10] Thus, unlike male circumcision, which is generally considered to be a

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[9] The statute provides that (subject to certain medical necessity exceptions) "whoever knowingly circumcises, excises, or infibulates the whole or any part of the labia majora or labia minora or clitoris of another person who has not attained the age of 18 years shall be fined under this title or imprisoned not more than 5 years, or both." Note, however, that an adult can consent to this procedure for herself. This is in line with the general rule that an adult can consent to virtually any legal medical treatment or procedure. (Criminalization of Female Genital Mutilation Act, 18 U.S.C. § 116 (2000)).

[10] CAL. PENAL CODE § 273.4; DEL. CODE ANN. tit. 11, § 780; 720 ILL. COMP. STAT. 5/12-34 (2002); MD. CODE ANN., HEALT–GEN. § 20-601; MINN. STAT. ANN. § 609.2245; N.Y. PENAL LAW § 130.85; N.D. CENT. CODE § 12.1-36-01; R.I. GEN. LAWS § 11-5-2(c)(3); TENN. CODE ANN. § 39-13-110; WIS. STAT. ANN. § 146.35.

safe procedure with some possible medical benefits, the female genital cutting is viewed in this country as both non-beneficial and harmful.

### Sex Assignment Surgery

A third case of elective sexual surgery is sex assignment surgery performed on minors. Studies show that nearly one out of every two-thousand children born in the United States is born with ambiguous genitalia [66]. An estimated one to two hundred pediatric sex assignment surgeries are performed each year [67]. The sexual assignment surgeries for children with ambiguous genitalia became an accepted standard of care in the 1970s. Most of these children underwent surgeries to create external female genitalia, and were raised as girls. Since the surgeries were performed on minor children, parents were the ones consenting to the procedure. Although there have been no definitive court decisions, in 1996 the American Academy of Pediatrics supported the idea of elective sex assignment surgery and recommended that it occur before the age of two-and-a-half years [68].

In the last decade, serious concerns have been raised about the efficacy of the sex assignment surgeries and the consequences such surgeries have on the patients. For instance, cases have been reported where the children who had sex-assignment surgery grew up unhappy with and confused about their assigned gender, and with psychological problems stemming from these feelings. The discovery of these harms, and the realization that sex-assignment surgery forecloses the "[c]hild's [r]ight to an [o]pen [f]uture," has led some experts and advocates to question the morality of parents consenting to sex-assignment surgery without any input by the children themselves. Nonetheless, the current standard of practice in the medical profession is to permit, and even to encourage, parents to quickly decide whether to assign a specific sex to a child with ambiguous genitalia. In the absence of statutes or court decisions to the contrary, this remains a legal practice, even though it permanently determines a child's sexual identity and the way the child will lead his or her life.

### Sterilization

A final case to consider is the parental decision to sterilize a child. Some parents wish to sterilize a daughter who is severely developmentally or mentally disabled because they believe that child bearing is not in the daughter's best interest, in part because she is unlikely to be able to care for her child, or perhaps even to understand the nature of pregnancy and childbirth [69]. Nonetheless, in most states, parents cannot make this decision on their own, even if the medical professionals agree with and recommend this course of action [70, 71]. Instead, most states require an independent judicial determination of the best interest of the child sought to be sterilized. The courts and legislatures have viewed sterilization "as an extraordinary measure which is to be decided by a court and undertaken only pursuant to court order" [72]. That is so because "[c]onsent by parents to the sterilization of their mentally retarded offspring has a history of abuse which indicates that parents, at least in this limited context, cannot be presumed to have an identity of interest with their children" [76, p. 370]. Generally, courts also require that there be "clear and convincing evidence" – a very high standard – showing that sterilization is in the child's best interests and that it is the least intrusive method of controlling the child's reproduction [73–76].

### Variations in Parental Consent Requirements

A common thread runs through the four situations just reviewed. It appears that the parental right to consent to surgery involving reproductive or sexual organs is highest when the procedure has identifiable (even if controversial) medical benefits and does not threaten the health or future reproductive choices of the child. Additionally, historical traditions as well as contemporary cultural and professional value judgments play a significant role in the acceptance or rejection of a procedure. Thus, parents are given virtually unfettered authority to consent to male circumcision because there are identifiable medical benefits to the procedure and because the procedure has been part of the Western tradition for close to 5000 years. Similarly, parents can consent to sex assignment surgery because the mainstream medical profession believes this surgery is necessary for a child's normal psychological and emotional development, despite contradictory evidence from recent studies. This perceived medical benefit is tied to dominant US social norms which dictate that individuals must have unambiguous external genitalia and sexual identities.

On the opposite side of the legal spectrum, female genital cutting is considered to offer no medical benefit of any kind, is foreign to Western traditions, and carries a high medical risk to the subject. Hence, parents are flatly prohibited from consenting to this procedure. The decision to sterilize an incompetent girl lies somewhere in between. Although the procedure arguably provides medical benefits by preventing a possibly harmful pregnancy, sterilization runs counter to US traditions that encourage reproduction and individual liberty. It also conjures up the sordid history of compelled sterilization of "feeble minded" and disabled persons during the eugenics era, which was discredited after World War II. Therefore, parents' request for sterilization is subject to approval by an independent judge.

## *How Does Current Law on Proxy Consent Apply to Oncofertility?*

The legal treatment of parental consent regarding the four elective surgeries discussed above can be used to create a framework for analyzing parental consent in the context of ovarian tissue cryopreservation.

The first consideration is the age of a child. If the child is still a minor but of an age at which she can comprehend some issues about future reproduction, she should be consulted. As the Oregon Supreme Court noted in *In re Marriage of Boldt*, at a certain age, decisions dealing with permanent alterations of the body may affect the relationship between the child and parent and could have a "pronounced effect on parent's capability to properly care for" the child [77]. Furthermore, other courts have recognized that mature (though not emancipated) minors, can participate in decisions about their healthcare, even if the decision is contrary to the commonly accepted medical practice [78–80]. Additionally, and as described above, courts and legislatures have long permitted minors to make decisions involving reproduction or sexual health with a reduced level of parental control over those decisions. Thus, in our view, to the extent possible, the views of the child must be solicited and, though not dispositive, be given due weight.

The second issue to be taken into account is the question of how much sexual function is likely to be retained post-surgery. For instance, if the procedure involves the removal of only one ovary, with the other remaining in place and being counted on to provide proper hormonal balance in the later years, there may be less concern than in cases where both ovaries are to be excised or where the ovary to be excised is the only healthy one. In the former cases, the risk to the patient is rather small, and the change in natural unassisted reproductive and ancillary sex functions is similarly small (though appreciable) [81]. In the latter cases, on the other hand, the chance of losing unassisted function is certain, and the child will need perpetual hormone replacement therapy [82]. In a situation such as this, a very careful balance must be made between the uncertain potential for future biological offspring versus the real and definite consequences of losing an organ that provides proper hormonal balance – and perhaps also reproductive function.

The third consideration is the size of the putative benefit of undergoing the chosen oncofertility procedure. It is worth remembering that at this stage the science of ovarian tissue removal for the purposes of future reproduction is at its infancy. No live births in humans have yet been reported following excision of an ovary and subsequent in vitro follicle maturation and fertilization [83].[11] However, live births in humans have been reported following excision of an ovary from tissue transplants and in vitro fertilization of available mature eggs [84–87]. It should be noted, that as of this writing, successful maturation of a human follicle to a mature egg capable of reproduction has been reported. Still, with regard to the preservation of human fertility, the protocol in question is at the early experimental stages. Importantly, since patients who are 5- or 6-years-old today will not be in a position to have children for another 15–20 years, it may well be that by then, the oocyte maturation process will be well established and will result in a level of success not below that which is expected for "regular" IVF protocols. Nevertheless, it must be recognized that at the present day, successful preservation of reproductive ability via ovarian tissue removal and storage is still under development.

The last issue to consider is the purpose of the parent's decision to subject the child to the ovarian tissue removal. To the extent that the parental decision is purely about preserving the child's future options, it is likely to be more acceptable to the legislatures, the courts, and the general public. As discussed above, much turns on whether the proposed medical procedure fits within US social traditions and norms.

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[11] However, studies on mice have resulted in live births. *See* Xu M, et al. Tissue-Engineered Follicles Produce Live, Fertile Offspring. *Tissue Engineering.* 2006; 12:2739–2746.

Because the ability to reproduce is generally valued in US society and is protected by the Constitution, preserving reproductive options is likely to be considered highly beneficial. In fact, the primary critique of the procedures discussed in these previous section is that they ignore "the [c]hild's [r]ight to an [o]pen [f]uture." Oncofertility procedures can be seen as preserving this right.

It can also be argued, however, that parents who seek ovarian excision & cryopreservation for their daughters are steering the child's future decisions toward child bearing. A child who undergoes ovary removal and preserves her ovarian tissue for a number of years may as a woman, feel enormous pressure to use the stored tissue. It provides a powerful reminder throughout the rest of her childhood and early adulthood of parental and societal expectations that she should one day bear children. Nonetheless, even if parental choices end up influencing the future choices of minors, such influence is legally permissible, as can be evidenced from a variety of decisions upholding parental rights to raise their children in a manner they deem appropriate.

On the other hand, consider the situation where the child has very little hope of recovery, yet the parents still wish to subject her to the ovarian tissue removal procedure in the hope of having a genetic grandchild from their soon-to-be-deceased child. When analyzed within the above-suggested framework, this hypothetical leads to a different result. In this situation, it cannot be fairly said that parents are preserving reproductive capacity and decisions that the child can exercise upon reaching the age of majority. The parents are preserving *their own* option of having a grandchild, but not their child's options (since the child is not likely to survive). In these circumstances, a court might decide that the parents are not acting in the best interest of the child, but are subjecting her to unnecessary medical procedures that carry no benefit either now or in the future.

## *Is Failing to Preserve Fertility the Same as Active Sterilization?*

The reverse side of the question of whether parents *can* consent to the ovarian tissue cryopreservation is the question of whether they *must* consent to it. Do parents have a duty to preserve their child's fertility if ovarian tissue cryopreservation is available? Do children have a right to the procedure even if their parents do not wish to consent to it? Although we cannot at this stage give any definitive answers, we will explore parents' potential legal obligations and outline the issues that ought to be taken into consideration when resolving these questions.

As discussed previously, parents are generally given wide latitude in deciding what constitutes appropriate medical treatment for their offspring. However, that latitude is circumscribed by the requirement that parents act in the best interest of the child consistent with not only the family's values and morals, but also with good medical practice and with "society's basic values."

The premise underlying parents' right to consent to ovarian tissue cryopreservation is that the procedure preserves the "basic" societal value of reproductive choice. It can be argued that children for whom parents give consent will be in a better – if not exclusive – position to exercise this choice compared to children whose parents did not consent. According to this view, parents who choose not to consent are depriving their child of her right to reproduce. In other words, it can be argued that parents' refusal to consent to a viable ovarian tissue cryopreservation is, in effect, no different than the parents' decision to sterilize their child – a decision that parents are not permitted to make without judicial approval. On the other hand, sterilization involves active medical intervention, whereas declining to consent to the ovarian tissue cryopreservation is passive non-interference. Whether this makes a difference in the legal outcome depends on a judgment about the moral equivalency of action and inaction in these cases [88]. That calculus may be affected by the eventual degree of success of ovarian cryopreservation.

In contemplating what the correct answer to the above dilemma should be, it is useful to weigh the factors discussed in the preceding section – the balance of medical risks and benefits, the societal acceptance of the practice, the effect on the child's "open future," and the success rate of the treatment.

To the extent that the minor in question can rationally consider her options and express her preferences accordingly, that should mostly be the end of the matter. Courts and legislatures routinely defer to mature minors' decisions on reproductive matters. Indeed, courts occasionally defer to minors even on life and death matters if the minor's decision is in accord with that of the parents, and if the minor is sufficiently mature. It stands to reason then that if minors can choose to terminate or to continue with pregnancy, their wishes will most likely be similarly honored with respect to the decision to preserve future fertility. Of course, this "easy" solution does not obtain when the minor is unable to rationally consider the various choices and come to an informed decision. Thus, the remaining two factors need to be considered.

First, the surgical risk of excising an ovary is minimal. In most cases, the procedure can be performed laparascopically. Although certain risks of infection and error are present, it is no greater than risk associated with any other surgical procedure (e.g., tonsillectomy). The low risk of the procedure, coupled with the low burden that it imposes on the minor, then militates toward the position that the procedure ought to be performed. On the other hand, the risk of being left without the ovary is significant. As discussed previously, loss of an ovary alters the hormonal balance and reduces the chances of in vivo pregnancy. This very real risk counsels against performing the procedure.

Second, presently, the success rate of using frozen ovarian tissue to obtain a live birth is speculative at best. But even if it were to become as successful as established IVF procedures, the success rate would still be quite low. If techniques using frozen ovarian tissue rise to the same level of success as IVF, it will no doubt be a tremendous achievement and a huge leap forward in terms of reproductive options available to young women stricken with cancer. That said, a 30% level of success may be insufficient to definitively require parents to take one or another course of action. On the other hand, if techniques using frozen ovarian tissue achieve significantly higher success rates (e.g., 80–90%), a much stronger case could be made that depriving the child of an opportunity to decide for herself whether or not to bear children later in life is a violation of the child's best interest and ought not be permitted.

The three factors outlined above, however, are not exhaustive, for they do not take into account individual family values that the parents hold and are likely to impart to their child. Parents are entitled to take their values into account in making medical decisions for their children. Moreover, the parents may place a higher priority on their child's current health than on their child's ability to become pregnant in the future. They may also oppose the use of reproduction-assisting technologies for religious, ethical, or cultural reasons. There is no doubt that the values imparted during the child's upbringing play a large role in the child's own decisions during adult life. Thus, for example, a child may grow up in a family that opposes procreation and instead supports adoption (because, say, they believe that the world is overpopulated). In that hypothetical family, the ability to reproduce in the future would not be particularly valued. Because this value is likely to be imparted on the child (who, given the hypothetical, would likely have been adopted), it is more likely than not that once grown, the child will not place a great premium on the ability to reproduce.

It is no answer to say that ovarian tissue cryopreservation simply preserves choice and does not actually force anyone to reproduce should they not want to. Subjecting the child to these medical procedures carries certain finite risks. It also is potentially distracting from the major issue facing the family – saving that child's life. Thus, the protocol is neither cost- nor risk-free. And the benefit that the protocol provides for the child of the hypothetical parents described above is, at best, questionable. Thus, deeply held family values should also be seriously considered and taken into account in deciding whether parental decisions not to consent are subject to judicial override.

The balance of factors, then, *at present*, counsels against disregarding parental wishes to forego ovarian tissue cryopreservation. However, as we stated in the beginning of this subsection, we cannot, with any confidence, predict how courts and legislatures will respond to this dilemma should it ever arise. By outlining this potential dilemma and discussing the factors that are likely to influence the answers, we are hoping to provide practitioners, patients, and the public a framework for the discussion of these questions.

## *Who Controls the Fate of the Excised Tissue While the Patient Is Alive?*

Once the gametes (whether sperm or ova) are harvested and stored (in whatever form) there is a question as to who controls the usage of this stored material. In cases of adults, the answer is clear. The control resides with the progenitor herself. The right to control the fate of one's gametes, whether these gametes are intra- or extra-corporeal, is firmly established in the law. As the Tennessee Supreme Court held in *Davis*, "the existence of the right [of procreational autonomy] itself dictates that decisional authority rests *in the gamete-providers alone*." Thus, a clinic cannot do anything with the stored gametes to which the progenitor has not agreed.

Children are at a disadvantage in this situation because they may not be able to express their wishes as to any disposition of the stored gametes, and to the extent that they are able to express them, such expression may not be legally binding while the children are minors. Nonetheless, we are of the view that the only people who should have the authority to decide the disposition are the children themselves, when they reach the age of majority. We come to this conclusion for several reasons.

First, the very premise of oncofertility treatment (whatever form it may take) is to preserve the patient's choices on whether or not to have children. Any decision by the guardian to donate or otherwise dispose of the child's gametes would vitiate the child's ability to make future choices. Hence, the initial procedure to preserve gametes would become useless, and therefore, in retrospect, would be improper, since it would serve no medical purpose whatsoever. Second, it is well established that children are not proper sources for live organ or tissue donation [89–95].[12] Therefore, parents should not be able to donate the child's gametes, just like they cannot donate a child's kidney or blood. Third, the parents' decisions with respect to the minors' medical treatment are limited by the requirement that the parents act in the best interest of the minor. When parents choose to dispose of minors' gametes, it is hard to see how they are acting in the minors' best interest. At best, such a decision neither advances nor detracts from minors' interests, and at worst, it runs directly contrary to those interests.

Finally, as we discussed above, parents are not permitted, without good cause and court approval, to forcibly sterilize their children. It seems to us that the prohibition applies whether the child's reproductive capacity is inside or outside the body. Any decision by the child's guardian that would destroy or significantly limit a child's existing reproductive capacity cannot be honored without the court's consent. Moreover, permitting someone other than the child to decide would create a dangerous risk of exploitation. For these reasons, we believe that once gametes are stored, the only person who can dictate their ultimate disposition is the donor. In those cases where the donor is a minor, the gametes must be stored until such time as the minor can legally direct their use or disposition.

## *Who Controls the Fate of the Excised Tissue When the Patient Is Dead?*

A more perplexing question regarding the ownership of excised and stored tissue arises if the patient dies. As discussed above, while the donor is alive, there is no question that she retains ownership of her tissue (unless she donated it to someone else) and that she can dispose of it as she wishes. The sad fact, however, is that far from all oncological patients win their battle with cancer. Once the patient dies, who should decide the disposition of the tissue that she left behind?

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[12] There is a very narrow exception for intra-family donations by minors when such a donation is necessary to save the life of another family member. Even blood donation by minors is limited.

The ovarian tissue cryopreservation protocol at Northwestern University presently employs a consent form where the patient agrees that, should she die, the tissue will be destroyed or donated to research. Needless to say, these options are not the only possible ones, nor are they likely to be acceptable to all patients. This is especially true when the patient herself is legally and/or mentally incapable of consent. There is, unfortunately, no American case law that directly governs the disposition of gametes after the donor's death. Several cases involving stored sperm have considered the wishes expressed by the deceased donor during the course of his life [96–98]. For example, in *Hecht v. Superior Court*, the California Court of Appeal decided a dispute between the decedent's adult children and his surviving girlfriend over the ownership of the decedent's sperm. The court held for the girlfriend because the decedent's will, along with other actions he took during his lifetime, clearly expressed the desire that the frozen sperm pass to his girlfriend. The *Hecht* court ruled that "'the seed of life . . .[is] tied to the fundamental liberty of a human being to conceive or not to conceive.' . . . [T]he fate of the sperm *must be decided by the person from whom it is drawn.* Therefore, the sole issue becomes that of intent."

This and other cases provide little guidance here because minor children are often incapable of expressing or even forming intent as to the future use of their gametes. Very young children simply do not (and cannot) know whether or not they would want children, let alone whether they wish to have post-mortem children. This inability to express any intent is especially acute in young female patients. As we have discussed, male patients are not candidates for gamete storage until the age of puberty. At that time, while they may not be able to fully appreciate the full meaning of fatherhood, at least they are able to express *some* preference about having children. Female patients, on the other hand, are candidates for gamete preservation at any time from birth on. Even newborn girls could theoretically be candidates for ovarian tissue removal and preservation. It is impossible to decide the disposition of tissue based on the intent of children too young to form or express an intent about childbearing. A different way of determining the disposition of the gametes must therefore be found.

There are three basic ways in which parents may wish to dispose of the ovarian tissue of a deceased daughter: it can be destroyed, donated for research,[13] or kept by relatives [14] for the purpose of having the decedent's child. It seems to us that either of the first two options is not problematic from the viewpoint of law or ethics. If the parents decide to destroy the tissue, it is really no different than deciding to bury their child's body without preserving any of her tissue – a decision countless parents make every day. Similarly, if the parents decide to donate the tissue to research, it

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[13] Tissue cannot be donated for transplantation with cancer patients because the risk of cancer re-seeding is too high [83].

[14] "Relatives" here is broadly defined to include blood relatives, relatives by marriage, and significant others who may not have been married to the decedent, but maintained a committed sexual relationship.

is no different than deciding to donate their child's body or organs for research – again, a decision that many parents currently make.

The third option, on the other hand, raises serious concerns. Although no American court has directly addressed the question of disposition of a decedent's genetic material absent clear expression of the decedent's intent, two French courts have done so. In *Mme. O. c. CECOS* [99], the wife's eggs were fertilized with her husband's sperm and stored. The husband died prior to implantation of the embryos and the wife requested that the embryos be implanted after his death. The consent form that the husband and wife signed prior to storing the embryos was silent on the question of disposition in cases of death or divorce. The High Court at Rennes, France, held that, absent proof that the husband intended his wife to be sole decision-maker with respect to the future of the embryos, the wife had no authority to unilaterally decide on implantation, whether pre- or post-death. The case of *Mme. P. c. La Grave Hôpital* [100] was similar to *Mme. O.*, except for the fact that the consent form signed by the husband and wife explicitly stated that consent of both parties is necessary for implantation. After the husband's death, the court upheld the agreement even though the husband's consent was no longer obtainable, thus declining to permit Mme. P. to proceed with implantation. As in *Hecht*, both French cases held that the intent of the progenitor is of paramount importance and is to be honored. Where the donor expressed no clear intent to become a parent, however, the courts will not infer it, even if the donor is deceased.

There is heated academic debate on the proper disposition of a decedent's genetic material. Although the debate focuses on the genetic materials that were stored by adult individuals (since childhood storage is a very new possibility), much of the logic can be applied to the problem of the disposition of stored genetic material of minors. For instance, John Robertson argues that "directions for *or against* posthumous reproduction deserve much less respect than decisions about reproduction when one is alive," thus concluding that the surviving relatives ought to control the disposition of the decedent's genetic material [101]. On the other hand, Professor Anne Schiff argues that whenever the decedent's wishes are unknown, a presumption against using gametes for posthumous reproduction should apply [102]. Professor Schiff concludes that "[r]espect for a person's autonomy requires that an individual's body or body parts not be utilized without that individual's prior consent," at least when not "justified by the compelling societal interest that exists . . . in saving lives and alleviating suffering."

Given the academic debate, we cannot predict how courts and legislatures would approach the issue of gamete ownership when the late progenitor has failed to express any wishes as to the disposition of the gametes. It seems possible that given the general reluctance of the courts both in this country and abroad to approve of non-consented reproduction, the default position may well be that the surviving family members will be prevented from using the deceased relative's gametes. On the other hand, given that the Uniform Anatomical Gift Act (the "UAGA") reposes the authority to donate the organs with the surviving relatives (unless the decedent expressed wishes to the contrary) [103], and permits the family to designate the recipient of those organs, the courts may permit family members to do as they desire.

What is clear is that the courts are honoring the written agreements made when the genetic material was stored. Thus, it is incumbent upon any clinic participating in the oncofertility program to develop a consent form where post-mortem options are listed and explained to the consenting parties. The list of options should be developed in consultation with the clinic's attorney in light of the laws of the jurisdiction and in consultation with a bioethicist. To the extent possible, the views of the minor should also be solicited as they may inform (though they may not be determinative) any decision on the fate of the stored gametes should the minor die.

## *Can Research on the Tissue Be Conducted and if So, What Steps Must the Researchers Take?*

Finally, we wish to consider the issue of research on the tissue that was excised to preserve the patient's fertility. The Oncofertility Consortium at Northwestern University asks the patient who has decided to freeze her ovarian tissue to donate 20% of that tissue for research. Participation in the program, however, is not predicated on consent and women retain the option to refuse to donate. Thus far, all women have consented to donate a portion of their ovaries to research. Nonetheless, there is always a possibility that some women may feel such pressure to donate that their consent is not truly voluntary. What are the conditions that would ensure that any consent to research on the excised tissues has been freely given?

As previously discussed, competent adult patients are free to dispose of their tissues as they will, including donating parts of it for medical research. Thus, overall, the guidelines with respect to obtaining tissue for research would parallel general guidelines on seeking patient's directives on tissue disposition. There must, however, be additional precautions to ensure that the decision made by the patient is truly free from any coercive effects. In our view, the guidelines of the UAGA are a good starting point in designing procedures meant to eliminate coercion.

Under the UAGA, a physician who attends the death of a donor is not permitted to be involved in the organ harvesting or transplantation because this may create a conflict of interest for the physician [103]. Though in the case of donating ovarian tissue the donor is not dead, a similar conflict may exist. The treating physician may have a conflict (or a perceived conflict) between focusing on treatment (whether oncological or fertility) and focusing on research. The physician may (at least theoretically) be swayed in his or her efforts depending on the patient's decision to donate or not donate parts of her tissue. Thus, taking the lead from the UAGA guidelines, it would be best if the donation were sought and obtained by personnel not involved with the treatment of the patient. Ideally, the treating physician should not know whether the patient chose to donate part of her tissue, lest his or her reaction to the decision affect the treatment provided to the patient.

Furthermore, in seeking the patient's consent to donation, physicians should disclose any financial interest they may have in the project. As the California Supreme Court noted in *Moore v. Regents of University of California*, in order for the consent to be truly free, a patient must rest assured that the treating physician is not improperly "influenced by a profit motive." As the court observed:

> A physician who adds his own research interests to this balance may be tempted to order a scientifically useful procedure or test that offers marginal, or no, benefits to the patient. The possibility that an interest extraneous to the patient's health has affected the physician's judgment is something that a reasonable patient would want to know in deciding whether to consent to a proposed course of treatment. It is material to the patient's decision and, thus, a prerequisite to informed consent [104].

It may be argued that in *Moore*, the court was concerned with procedures being done to the patient in vivo in order to bolster the research being done in vitro and that the same concerns do not apply to oncofertility research that would involve tissue already voluntarily excised from the patient. Thus, the argument goes, the donation to research would not subject the patient to any additional risks, the researcher would not have a conflict of interest, and therefore the patient would not need to take that conflict into consideration in deciding whether to consent to research. While the observation that in vitro research does not necessarily involve any risk to the patient or conflict of interest for the researcher is correct, this argument does not apply to oncofertility research. For one thing, oncofertility patients, unlike the patient in *Moore*, do not have diseased organs, for which they have little use, excised. Rather, oncofertility patients preserve their tissues precisely because they expect to use them in the future. Thus, they may be disinclined to surrender any part of that tissue for fear that such surrender would diminish their chances of having a child. Furthermore, the conflict of interest may still be present. The tissues are excised in order to preserve fertility and the ability to have children in the future; therefore, the primary concern of physicians should be helping their patients conceive when and if they desire to do so. Pursuing their own research interests may conflict with physicians' responsibility to treat their patients' infertility.

For the reasons outlined, it is critical that oncofertility programs adopt strong guidelines that ensure that patients can make truly informed and uncoerced decisions about whether or not to donate their tissues to research.

## *Are There Additional Concerns?*

This chapter is by no means an exhaustive treatise on the legal, moral, and ethical questions that surround the field of oncofertility. Questions of financing, religious objections, and access must be considered by both those who set up oncofertility programs and those who decide on public policy concerning them. The Oncofertility Consortium continues to examine these issues and we expect that future scholarship by other members of the Consortium will expand the analysis we provide here.

## Conclusion

The emerging field of oncofertility holds out new hope and possibilities for individuals whose fertility may be compromised by disease of reproductive organs or medical treatment. With further advances in the science, the patients will retain the ability to have children and to exercise their freedom to make reproductive decisions. However, as science develops, the scientists and physicians also acquire responsibilities to make sure that these advances are not used in an unethical or illegal manner. This chapter attempts to outline several difficult problems that oncofertility practitioners, patients, and patients' families are likely to face. We hope that our analysis will stimulate needed discussion in the laboratories, clinics, and at the bedside, and that through this ongoing dialogue, strong ethical and legal guidelines will emerge.

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# Chapter 10
# Domestic and International Surrogacy Laws: Implications for Cancer Survivors

**Kiran Sreenivas and Lisa Campo-Engelstein**

## Introduction

Much of the focus in the new field of oncofertility has been on preserving cancer patients' fertility prior to treatment that is likely to diminish their fertility or render them sterile. Less attention, however, has been paid to the logistics of using frozen eggs, embryos, or ovarian tissue following cancer treatment. It is usually assumed that, following some manipulation, the frozen eggs, embryos, or ovarian tissue will be transferred back into the women's bodies via assisted reproductive technology (ART) so that they can become pregnant. Some women, however, cannot utilize this technology because their cancer treatment has left them unable to gestate. If these women desire biological children and have banked eggs, embryos, or ovarian tissue, then the only option available to them is surrogacy. Our goal in this chapter is to examine the availability of surrogacy[1] to cancer patients. To this end, we will provide an overview of both domestic and international surrogacy laws and discuss their impact on cancer survivors and others seeking surrogacy.

This chapter is divided into five parts. In the first part, we present the types of cancers and cancer treatments that can leave a woman unable to gestate. In the second part, we outline different types of surrogacy arrangements. The third part is where we examine surrogacy laws in the United States, explaining how early surrogacy cases led to different state laws. We explore international surrogacy laws in the fourth part, categorizing them by degree of regulation and highlighting one country that exemplifies each category. In the last part, we discuss surrogacy tourism as an option for cancer survivors and underscore the importance of fully informing cancer patients about surrogacy, including potential legal barriers in utilizing it, before they make fertility preservation decisions prior to cancer treatment.

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[1] It is important to note that we are only dealing with the legal side of surrogacy. We are not making any normative claims about the morality of surrogacy.

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## The Inability to Gestate Due to Cancer and Cancer Treatment

Various cancers and cancer treatments can result in a woman being unable to gestate. Frequently, one of five types of gynecologic cancers (uterine, ovarian, cervical, vaginal, and vulvar) is the underlying cause. In the United States and similarly developed countries like France, uterine cancer tends to have the highest incidence rate of the group. In lesser developed countries like Brazil and India, it is not uncommon for the incidence of cervical cancer to be higher than that of uterine cancer (See Fig. 10.1) [1]. Like most cancers, the three main treatment options for gynecologic cancers are surgery, radiation therapy, and chemotherapy (or any combination of the three). Given their location, any form of treatment for gynecologic cancer has the potential to prevent a woman from safely carrying a fetus to term.

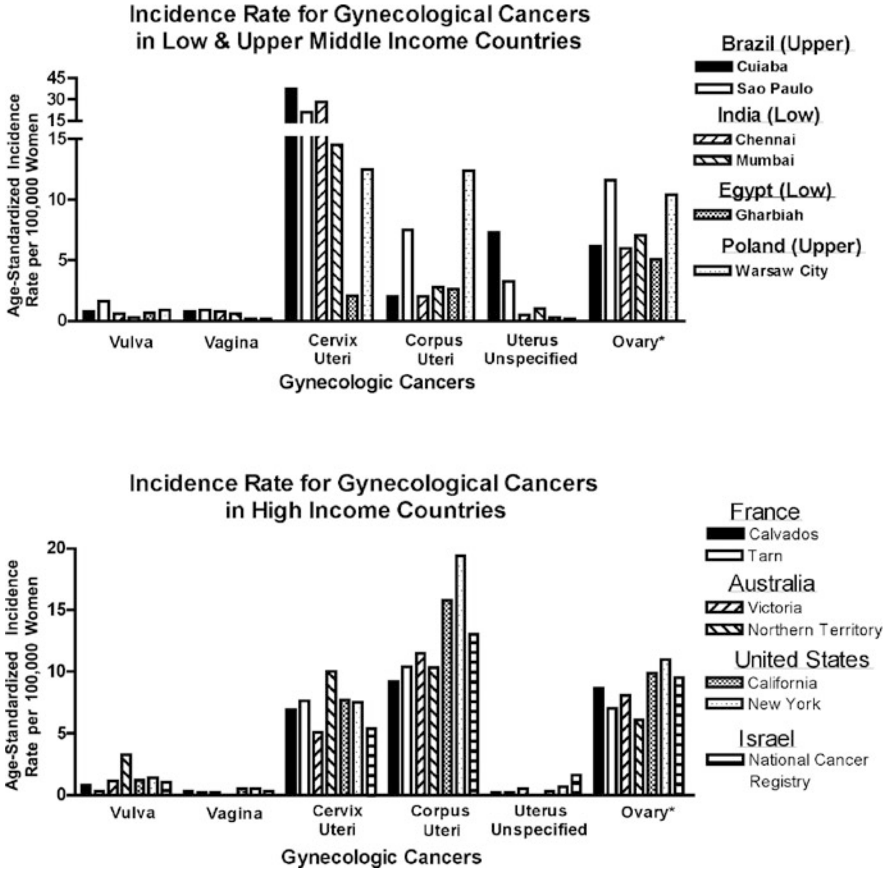

**Fig. 10.1** Incidence of gynecological cancers around the world. * – Special care should be taken in comparing ovarian cancer incidence rates because of recent changes in coding and classification. See original source for more details. *Age-Standardization* – See original source for the demographics of the population used for standardization. Sources: *Incidence Rates* – Curado et al. [1] *Country Income Classifications* – The World Bank, July 2009 (http://go.worldbank.org/D7SN0B8YU0)

Surgery for gynecological cancers can entail a hysterectomy – the removal of the uterus – thereby eliminating any possibility of gestation. Under certain conditions, a hysterectomy may be performed to prevent cancer. Endometrial hyperplasia, a condition in which there is an increase in the number of cells lining the uterus, is one example [2]. Some surgical procedures, however, allow for the possibility of gestation. For instance, a woman who has undergone a radical vaginal trachelectomy (the removal of the cervix, part of the vagina, and the lymph nodes in the pelvis) may be able to experience pregnancy [3]. However, women who have had this procedure have been observed to have a high rate of delivering prematurely [4].

Radiation to the pelvic area to treat gynecologic cancers increases the risk for pregnancy-related complications. Such complications include spontaneous miscarriages, preterm labor and delivery, low-birth-weight infants, and placental abnormalities, and their likelihood is dictated by the dosage and specific location of the radiation. There are several explanations for the occurrence of these complications. First, radiation may cause a reduction in the size of the uterus. Second, possible uterine vasculature damage may lead to decreased fetoplacental blood flow. Third, damage to tissue may prevent the uterus from being able to accommodate the growth of a fetus. As cancer continues to be detected at younger ages, it is important to note that the negative effects of radiation on the uterus are thought to be greater in prepubertal girls [5].

For radiation therapy not directed in the pelvic area, there is potential risk of hindering fertility if the hypothalamic-gonadal hormonal axis is altered or damaged. This axis helps regulate the hormones estrogen and progesterone, which play key roles in regulating menstruation and maintaining a viable uterus [5].

Chemotherapy can affect fertility in a similar fashion by altering hormone regulation. Tamoxifen, a chemotherapeutic agent used to treat breast cancer, has been found to increase a woman’s risk for uterine cancer by causing an increase in estrogen production [6]. The use of Tamoxifen as a chemopreventive agent for those with an elevated risk of developing breast cancer has risen. However, it is not the only cancer preventative measure that can affect fertility. Women with BRCA mutations may decide to have their ovaries removed to reduce their risk of ovarian cancer thus causing them to rely on IVF (in vitro fertilization) or surrogacy to have a biological child.

In various international clinics, the most common reason why women pursue surrogacy is because of a hysterectomy (see Table 10.1) [7–9]. Consequently, as our society continues to be more active and aggressive in treating cancer, it is important that patients who have had a hysterectomy are knowledgeable about the available fertility options, including surrogacy. However, surrogacy is not always an easy option due to various domestic and international laws.

## Types of Surrogacy

With advancements in the preservation and transferring of gametes, surrogacy (along with other ART) has further challenged how we define parents. Today, there are three parental roles in any surrogacy agreement. The first is the role of the

**Table 10.1** Indications for treatment by IVF surrogacy around the world

| | British clinic [7] | American clinic [8] | Australian clinic [9] |
|---|---|---|---|
| Following hysterectomy (%) | 48 | 45.5 | 40 |
| Damaged or congenital absence of the uterus (%) | 17 | 13.4 | 24 |
| Repeated failure of IVF treatment (%) | 17 | N/A | 16 |
| Recurrent miscarriage (%) | 13 | N/A | 8 |
| Severe medical conditions incompatible with pregnancy (%) | 5 | N/A | 12 |
| Total number surrogacies | 37 | 112 | 25 |

intended or social parents. These are the people who intend to raise the child; they are the ones usually considered the child's legal guardians. Both women and men can be social parents and most children have one or two social parents. Second, the biological parents are the ones who are genetically related to the child. Every child has exactly one biological mother and one biological father. The third role is that of the birth or gestational mother, that is, the woman who carries the fetus and ultimately gives birth to the child. There can only be one birth mother and no birth father since men cannot experience pregnancy. An individual can fulfill one or more of these parental roles.

While there are numerous possible permutations for fulfilling these roles, there are two common surrogacy arrangements. The first is traditional surrogacy, where the surrogate or birth mother is also the biological mother and the intended father is also the biological father. In this situation, the surrogate mother is usually artificially inseminated with the intended father's sperm. Before IVF became broadly available, traditional surrogacy was the only type of surrogacy infertile couples could use. For many heterosexual couples, the significant disadvantage of this type of surrogacy is that the intended mother is not also the biological mother. As IVF became more common and accessible to the general public, another type of surrogacy burgeoned: gestational surrogacy. The only difference between this type of surrogacy and traditional surrogacy is that in gestational surrogacy the birth mother is not genetically related to the child. In both arrangements, the intended father and the biological father are the same person, unless donor sperm is used. IVF made gestational surrogacy possible because of an improvement in technology: physicians are now able to remove an egg from the intended mother, fertilize it with the sperm of the intended father, and then implant the resultant embryo into the uterus of another woman.

In addition to differentiating surrogacy by parental roles, surrogacy can also be classified into two types based on financial compensation. The first is altruistic surrogacy, in which the surrogate is not financially compensated for her role, though the intended parent or couple may cover any fees and costs associated with bringing an embryo to term. This type of surrogacy is most common among family members or close friends (e.g., a woman serving as a surrogate for her sister). The typical reason given for why no financial compensation is needed is that, in this type of surrogacy, the decision to be a surrogate stems from love, not from personal gain or even avarice. While the language of generosity is often employed in the other type of surrogacy – commercial surrogacy – the surrogate is financially compensated beyond expenses associated with the pregnancy. That is, the surrogate is paid for her gestational "services." Gestational surrogacy is typically arranged by surrogacy agencies, which collect a fee from intended parents and are responsible for the exchange of money between intended parents and surrogate.

Given the complexity of surrogacy arrangements, especially when money is involved, most people enter into contracts to ensure that all actors are aware of, and will adhere to, the rules and their responsibilities. Indeed, the purpose of a surrogacy contract, like any other type of contract, is to form a legal obligation for the involved parties to meet certain expectations and to provide legal recourse if they do not. However, the legality and enforceability of such an agreement varies not only from country to country, but also from state to state within countries like the United States and Australia. In the next sections, we will discuss the laws surrounding surrogacy in both the United States and for select international countries, exploring the social and political explanations for such laws and examining their impact on those seeking surrogacy, especially cancer survivors.

## Surrogacy Laws in the United States

In this section, we will provide a brief history of the most influential surrogacy cases in the United States that established precedent for the surrogacy laws (and lack thereof) we have today. The first recognized surrogate arrangement in the United States was in 1976; from then to 1988, there were roughly 600 children born as a result of surrogacy [10]. During this time, surrogacy arrangements were generally covert and inconspicuous, with limited attention from the media and no legal regulation.

This all changed when the now infamous Baby M case garnered national attention from 1986 to 1988 [11]. William and Elizabeth Stern, a couple from New Jersey, sought gestational surrogacy because they feared pregnancy would exacerbate Elizabeth's multiple sclerosis. However, gestational surrogacy was not readily available in 1984 because IVF was in its infancy. They settled on traditional surrogacy, consulted with Noel Keane's Infertility Center of New York, and were matched with Mary Beth Whitehead in January 1985. A contract was drafted stating that for ten thousand dollars plus expenses, Whitehead would be artificially inseminated with William's sperm and upon birth, she would relinquish her maternity rights and give the child to William [12]. In addition to this contract, Whitehead handwrote a Declaration of Intent which stated that it was in the best interest of the baby for William to have "immediate and uncontested custody" [13, p. 129]. Accordingly, Whitehead agreed to name William as the father on the birth certificate and to let the Sterns name the child [13].

However, when Whitehead gave birth on March 27, 1986, things went amiss. Instead of listing William as the father, Whitehead listed her husband and named the baby Sara Elizabeth, rather than Melissa as the Sterns had requested. Because William was not named as the father on the birth certificate, he had no legal claim to the baby. Regardless, 3 days after giving birth, Whitehead gave the Sterns custody of the baby. Whitehead, however, soon regretted doing this, and out of fear, the Sterns allowed Whitehead temporary custody [12]. Refusing to return the baby in exchange for the money the contract promised, Whitehead threatened to flee if court action was pursued. This threat did not stop the Sterns from going to the county court on May 5 to enforce the surrogacy contract [13]. When the judge ordered Whitehead to return the baby to the Sterns, Whitehead acted upon her word and fled to Florida with the baby, threatening to kill the baby if the issue was not dropped [12]. She was not found until July, and the baby was then returned to the Sterns [13].

Whitehead and the Sterns went to court to determine parental rights. In a lower court, a New Jersey judge declared their surrogacy contract valid and enforceable. Consequently, the judge terminated Whitehead's parental rights (though she was given limited visitation rights), which allowed Elizabeth to legally adopt the baby. On appeal, the New Jersey Supreme Court found the contract to be unlawful because it violated the prohibition against financial compensation for children, a law originally designed for adoption cases. Furthermore, the Supreme Court ruled that surrogacy cases should follow adoption laws, which typically allow pregnant women the legal right to reclaim full custody of the child within a given period of time. Whitehead reclaimed her maternity rights, invalidating Elizabeth's parental rights. However, William was granted full custody based on the best interests of the child. Because Whitehead had parental rights, she was granted uninterrupted and unsupervised visitation rights [13].

Only a few years after the Baby M case – from 1990 to 1993 – another surrogacy case from California was in the national spotlight: *Johnson v. Calvert*. While this case also involved a surrogate, Anna Johnson, seeking custody of the child from the intended parents, Mark and Crispina Calvert, it differed in three significant ways from the Baby M case [11]. First, gestational surrogacy was performed instead of traditional surrogacy. California law only recognizes one mother, and motherhood is based on who gave birth to the child and who is genetically related to the child. In most cases, the birth mother and the genetic mother are the same person. In this case, however, Johnson was the birth mother while Crispina Calvert was the biological mother. The lower court, as well as the California Supreme Court, gave custody to the Calverts on the basis of intent. Specifically, the Supreme Court argued that when there is a conflict between the birth mother and the genetic mother, the woman "who intended to procreate the child – that is, she who intended to bring about the birth of a child that she intended to raise as her own – is the natural mother under California law" [13, p. 360].

Second, the agreement between Johnson and the Calverts was made without a broker. Some claim that the absence of a broker partially explains why a disagreement over the custody of the child materialized. According to this line of thought, brokers screen potential surrogates to ensure that they are emotionally equipped to give up the baby at birth. For instance, many people lauded California broker Bill Handel and his Center for Surrogate Parenting for their stringent screening process, which they saw as the reason why "none of the center's 141 surrogate births has wound up in court" [13, p. 122]. Some believed Johnson's strong desire or need for financial compensation blinded her from the potential difficulties she might face in relinquishing the child and that this is something a broker would have noticed and taken into account when considering if she should be hired. Using a broker does not necessarily obviate concerns about possible broken contracts. Keane, the broker hired by the Sterns, was scrutinized for his lax surrogate screening process in the media. Keane's image was tarnished to the point that, reportedly, the main impetus for Michigan outlawing surrogacy contracts was a state senator who wanted to shut down a surrogacy clinic in Dearborn, Michigan run by Keane [11].

Third, the media presented these two cases in different ways. According to an analysis done by Susan Markens, editorials in the *New York Times* (which more intensely covered the Baby M case) tended to equate surrogacy with "baby selling," whereas editorials in the *Los Angeles Times* (which focused more on *Johnson v. Calvert*) often framed surrogacy as a "plight of infertile couples." These different media perspectives can be linked to the aforementioned specifics of each case. In the case of Baby M, surrogacy was not a last resort for the Sterns. As published studies before and during the 1980s show, pregnancy does not detrimentally affect women with multiple sclerosis [14]. Additionally, the use of a broker and its associated fees highlighted the commercial aspects of surrogacy beyond compensation to the surrogate. In *Johnson v. Calvert*, the only option the Calverts had if they wanted a genetic child was surrogacy because Crispina had undergone a hysterectomy. Since the Calverts did not use a broker, the commercial aspects of surrogacy were not as blatant. The main impact of these varying media reports on the details of each case was on how public opinion in the local area was shaped, thus leading to geographic differences in how people view surrogacy [11]. These differing geographic opinions are reflected in the state laws. New York has statutes that ban surrogacy contracts and make it a criminal offense to broker contracts or engage in commercial surrogacy. In contrast, California has no state legislation regarding surrogacy, thereby leaving the courts to solve individual conflicts [15].[2]

In addition to media coverage of these surrogacy cases, another contributing factor to the geographically diverging surrogacy laws is the public's view on family law. For example, California was the first state to implement the no-fault divorce and has a community property standard that requires any assets acquired while married to be split evenly upon divorce. These laws reflect an understanding of

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[2] It is interesting to note that Marken's theory – the way the local media framed surrogacy influenced state laws – may not be as relevant today as it was in the late 1980s and early 1990s due to the explosion in global media outlets, particularly the internet. If a controversial surrogacy case emerged today (perhaps one involving international surrogacy since the United States does not have laws to handle these arrangements), editorials, especially in the form of blogs, would probably be written by people all over the country, and perhaps the world, not just the local area. One can question how these presumably heterogeneous views would shape and change local laws.

marriage and family as a contractual and commercial relationship, so permitting surrogacy contracts coheres with these existing laws. New York's family laws do not reflect the same values of California. New York followed California in adopting a no-fault divorce option, but New York's law that requires couples to be separated for a year before divorce is granted illustrates that marriage is viewed as more than a contractual agreement in New York state [11].

As the comparison of New York and California shows, the legality and enforceability of surrogacy contracts can vary dramatically from state to state. Each state has to determine how they want to regulate surrogacy because there is no federal legislation, though there was a push for it following both the Baby M and *Johnson v. Calvert* cases. Surrogacy laws can be categorized into three categories. The first category is comprised of laws that permit surrogacy contracts by outlining the criteria for the contracts to be lawful and enforceable. For example, surrogacy laws in Florida require that the intended couple must be over 18 years old and married, the intended mother must be incapable of gestating a pregnancy without physical risk to herself or the fetus, and at least one of the intended parents must be biologically related to any resulting child. These requirements have to be fulfilled in order for any surrogacy contract to be legal and enforceable [15].

Rather than enumerating the necessary criteria for surrogacy contracts to be legal and enforceable, laws in the second category do the opposite by stating what is *not* legal with regards to surrogacy, such as commercial surrogacy, advertising for surrogacy, or getting paid to broker a contract. One drawback of these laws is that they do not address the legality of surrogacy contracts that do not violate the restrictions. In Kentucky, for example, statutes deny the enforceability of surrogacy contracts when compensation is given to the surrogate or if an attorney or agency is paid to negotiate the contract. However, these statutes are not clear about covering the ordinary expenses associated with a surrogacy and they only directly refer to traditional surrogacy. Therefore, it is unclear if altruistic and gestational surrogacy is also illegal [15].

Unlike laws in the first two categories, laws falling under the third category are clauses that mention surrogacy in the context of other civil laws. Like the secondary category, these clauses fail to take a clear stance on surrogacy. For example, Iowa and Alabama have included clauses within their adoption law that forbids payments in adoption proceedings in order to allow surrogates to be financially compensated. In Wisconsin, a statute was passed that outlines how a birth certificate should be issued in the event that a surrogate gives birth. The legality and enforceability of surrogacy contracts is not addressed in this or any other Wisconsin statute [15].

These categories are not mutually exclusive, so laws can fall into two or more of these categories. For example, a surrogacy law in Louisiana stipulates that a surrogacy contract can be enforceable as long as no financial payments are made. This law falls into the first two categories because it outlines how to make a surrogacy contract legal and states what is not allowed with regards to surrogacy [15].

Challenging the constitutionality of laws that restrict surrogacy has not yielded positive results. Two court rulings in Michigan attest to this outcome. In *Doe v.*

*Kelly*, the constitutionality of a statute that banned compensation for adoption, including within surrogacy arrangements, was challenged on the basis that it hinders a person's right to procreate. The statute was found to be constitutional because it still allowed altruistic surrogacy and uncompensated adoption. In *Doe v. Att'y Gen*, the constitutionally of a law that outright banned surrogacy agreements was brought into question on the basis that it violated private, procreative decisions. The court affirmed the constitutionality of the law in question by claiming it is preventing the commodification of children, promoting the best interests of children, and preventing the exploitation of women [15].

Finally, some states do not have any laws dealing with surrogacy. Recognizing the complexity of surrogacy, especially the numerous possibilities for surrogacy contracts, some states have concluded that legislation is not the best way to address this issue. Consequently, courts have been left with the burden of resolving conflicts and dictating informal policies within these states. Many courts defer to precedents set by Baby M and *Johnson v. Calvert* to resolve surrogacy disputes, such as looking specifically at whether surrogacy arrangements follow adoption laws, the best interests of the child, and who the intended parents are. These precedents have also been a guideline for some states with regards to their statutes on surrogacy. For example, Arizona and Indiana explicitly make surrogacy contracts unenforceable so surrogacy can follow adoption laws in allowing the surrogate to change her mind and keep the baby within a certain timeframe after giving birth [15] (For a summary of state laws see Table 10.2).

## International Surrogacy Laws

Having explored surrogacy on the domestic level, we now turn to the international level. Just as states in the US have surrogacy laws based on their views of surrogacy, so too do countries. We have separated international approaches to surrogacy into three categories – free market, regulated, and prohibited – and examine one country in each category – India, Israel, and France, respectively.

### *Free Market*

A free market approach permits surrogacy with limited or no government regulation. This is akin to states in the United States that have no laws or statutes regarding surrogacy. With this approach, individuals, brokers, and clinics, rather than the government, determine what appropriate measures need to be taken in order to protect all involved parties.

India epitomizes the free market approach to surrogacy. Since commercial surrogacy was legalized in 2002, nonbinding suggestions from a government sponsored medical research council have been the basis for the little regulation that is present for surrogacy [16]. This has resulted in there being few restrictions on who can

**Table 10.2** Summary of domestic surrogacy laws

| | Regulates surrogacy contracts | Refuses to enforce contracts | Bans commercial surrogacy | Exempts surrogacy from baby-selling statues | Allows "reasonable" payment to surrogate | Prohibits a third party from brokering a contract |
|---|---|---|---|---|---|---|
| Alabama | | | | X | | |
| Arizona | | X | | | | |
| Arkansas | | | | | | |
| California | | | | | | |
| District of Columbia | | X | X | | | |
| Florida | X | | X | | | |
| Illinois | X | | | | X | |
| Indiana | | X | | | | |
| Iowa | | | | X | | |
| Kentucky | | X[2] | | | | X |
| Louisiana | | X[2] | | | | |
| Maryland | | Z[2] | | | Z | |
| Massachusetts | Y[4] | Y[4] | | | Y[5] | |
| Michigan | | X | X[3] | | | |
| Nebraska | | X[2] | | | | |
| Nevada | X | | X | | | |
| New Hampshire | X | | | | | X |
| New Jersey | | Y | Y | | | |
| New York | | X | X | | | X |
| North Dakota | | X | | | | |
| Ohio | | | | | | |

**Table 10.2** (continued)

| | Regulates surrogacy contracts | Refuses to enforce contracts | Bans commercial surrogacy | Exempts surrogacy from baby-selling statues | Allows “reasonable” payment to surrogate | Prohibits a third party from brokering a contract |
|---|---|---|---|---|---|---|
| Oregon | | $Z^4$ | | | Y | |
| Pennsylvania | | $Y^5$ | | | | |
| Utah | X | | | | X | |
| Virginia | X | | X | | | |
| Washington | | $X^2$ | X | | | X |
| West Virginia | | | | X | | |
| Wisconsin | | | | | | |

*States with no statues addressing surrogacy*: Alaska, California, Colorado, Connecticut, Delaware, Georgia, Hawaii, Idaho, Kansas, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Missouri, Montana, New Jersey, New Mexico, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Vermont, Wyoming.

Key: X – State Statute; Y – Court Precedent; Z – Attorney General Opinion; 2 – Commercial Surrogacy; 3 – Altruistic Surrogacy; 4 – Traditional Surrogacy; 5 – Gestational Surrogacy.

Sources: Kindregan and McBrian [15]; Rao [22].

partake in surrogacy (e.g. homosexual couples can use a surrogate) and has led to more flexibility in legally defining parents. For instance, a surrogate can relinquish her motherhood rights before giving birth and not have her name be on the original birth certificate. Additionally, it enables each clinic to be self-regulated and implement independent policies to assure a smooth transaction. The Center for Human Reproduction in India, for example, does not permit contacts between the egg donor, surrogate mother, and the future parents. The Center only practices gestational surrogacy because of the belief that the surrogate will be less likely to form a bond with the child [17].

## *Regulated*

A regulated approach condones surrogacy so long as it follows specific parameters. Countries with this approach fear that if left unregulated, surrogacy will likely violate public interests and cultural values. Government regulation, therefore, is necessary to restrict who can partake in surrogacy agreements and/or what types of surrogacy are permitted.

Israel, for example, has a regulated approach to surrogacy, which was achieved with the passage of the Surrogate Motherhood Agreements Law in 1996. As part of this law, the Committee for Approving Surrogate Motherhood Agreements was established to pre-approve all surrogacy agreements and ensure their adherence to regulations in order to protect all parties involved in surrogacy. In addition to written legislative surrogacy regulations, there are precedents set by the committee that serve as unofficial regulations for surrogacy contracts [18].

Israel has several regulations regarding surrogacy to protect a variety of agents: society and social values, future children, surrogates, and intended parents. While many of the following regulations also benefit individuals, their main purpose is to uphold specific social values. Some restrictions deal with who can enter into a surrogacy contract. For example, only couples with medical justification can use surrogacy; surrogacy cannot be used for convenience or cosmetic reasons. In addition, couples who already have two children are automatically denied. Moreover, only Israeli residents are allowed to enter into an agreement with a surrogate and establishing residency is not an easy task. The contract review committee recommends that couples interested in surrogacy wait at least 18 months after immigrating to Israel before submitting a surrogacy application. Another important restriction on who can enter into a surrogacy agreement is due to the taboo on incest: a surrogate cannot be related to the intended parents. Other restrictions address the types of surrogacy arrangements permitted. For instance, the intended father's sperm must be used in order to respect Jewish law to ensure the child's paternity is known. Also, traditional surrogacy is illegal because it seen as akin to adultery [18].

In addition to restrictions to uphold social values, there are also regulations that seek to protect individuals, such as the future child. The interests of the intended child are served by requiring what is thought to be the most ideal living arrangement for a newborn. This includes allowing only heterosexual couples who are married or living together to be the intended parents. It is also required that the father be younger than 59 and the mother be younger than 48 [18].

Third, some regulations are intended to protect surrogates by restricting who can serve in this role. Surrogates must be older than 22 but younger than 40, must have given birth no more than five times, and must have undergone a maximum of two Cesarean sections. An unofficial restriction established by the Committee is that a surrogate has to have given birth to at least one child so that she knows from firsthand experience what pregnancy involves, which will hopefully give her a better idea of whether she will be able to relinquish the baby. To protect surrogates' health, they undergo mandatory physical and psychological examinations. The results of these examinations are included in a woman's application to become a surrogate. Once a surrogate gives birth, she is entitled to 6 months of counseling paid for by the intended parents. A surrogate's legal rights are supported by mandatory legal council from a lawyer independent of the intended parents [18].

The rights of the intended parents are protected by oversight from the Committee. Intended parents are not only permitted to provide compensation above the costs of all the medical procedures, but are also expected to because surrogates give their time and may undergo suffering. The Committee must approve compensation – by requiring preapproval for all compensation, it is thought that the intended parents are protected from extra demands by the surrogate before, during, and after the pregnancy. The parents are further protected by the requirement that the surrogate must appeal to the committee if she changes her mind and wants to keep the child at any point during the process. It is believed that the Committee will rule in the best interests of the child if such a dispute ever arises [18].

## *Prohibition*

A third approach is a legal ban on all types of surrogacy. France is one country that has taken this approach, outlawing surrogacy with the 1994 Act on Bioethics. France's position on surrogacy has been reaffirmed through additional court cases and legislation. The impetus for banning surrogacy in France was a 1991 court case involving an altruistic traditional surrogacy. The surrogate gave birth anonymously, which is legal, in order to forgo her claim of motherhood. While the intended father was able to assume custody of the child through his genetic relationship, the intended mother, who was not genetically related to the child, was unsuccessful in her adoption attempts. A lower appeals court found the surrogacy contract legal and granted the adoption. However, the higher court overturned the decision, ruling that surrogacy violates the principle of inalienability of the human body and the principle of inalienability of individual status [19].

A 2002 court case upheld France's ban on surrogacy. In this case, a French couple, Emmanuel and Isabelle, entered into a contract with a gestational surrogate in California. After the resultant twin girls were born, the couple brought the twins back to France and tried to legally adopt them. The French consulate in California was wary of this arrangement and notified officials back in France. Traditionally, when French authorities suspect that an adoption stems from a surrogacy contract, they allow fatherhood to be claimed through genetic tests. For motherhood, however, genetic contribution does not outweigh the bond created through pregnancy. In Isabelle's case, therefore, proceedings in France led to the nullification of her declaration that she was the mother of the twins. A French court could grant a woman in Isabelle's position a partial adoption, which restricts a parent's legal rights to the child. Not having full legal or custodial rights can be problematic for a mother if the couple gets a divorce or the father passes away, as the child may not be awarded to her [19] (For a summary of international laws see Table 10.3).

## Options for Cancer Survivors: Surrogacy Tourism

As our discussion of domestic and international surrogacy laws shows, the ability to use surrogacy varies widely. What does this mean for cancer survivors who are unable to gestate? In short, a cancer survivor's ability to use a surrogate greatly depends on her geographic location.[3] Surrogacy tourism has emerged to fill the need of those wanting to use surrogacy, but living in a place where it is highly regulated or banned. Domestic surrogacy is one option for those within the United States: people living in a state that bans surrogacy may set up a surrogacy arrangement in a nearby state that permits it. However, the enforceability of such an arrangement is unclear among most states as there are few laws that specifically address this issue. Washington is one state that has addressed the issue by making commercial surrogacy arrangements within and outside the state unenforceable to its residents [15]. International surrogacy is another option, and this option extends to people in countries where surrogacy is highly regulated or banned is international surrogacy. Even people in places with a limited regulatory or a free market approach to surrogacy sometimes opt for international surrogacy because it is much cheaper than domestic surrogacy. India, for example, is an attractive destination for surrogacy tourism for precisely this reason. The average cost of a surrogacy arrangement in India is approximately $25,000, which is significantly cheaper than a conservative estimate of $70,000 in the United States. The price for Indian surrogacy covers all medical procedures, payment to the surrogate, as well as airfare and hotel accommodations for two trips (the first trip to implant the embryo and the second one to collect the baby). The lower cost in India makes surrogacy a more feasible option for individuals or couples of a lower socioeconomic class. In addition to the lower cost, India, as discussed, has very few regulations on surrogacy and allows surrogates to waive their parental rights before birth, thus giving intended parents a higher level of assurance that they will receive the baby [17].

Although international surrogacy tourism may be the only option or a more attractive option for some, it can run into serious legal complications when the

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[3] Some may argue that geography should not determine one's ability to use surrogacy. They may claim that this raises various justice concerns. These concerns are outside the scope of our chapter.

**Table 10.3** Summary of international surrogacy laws

| | Gestational surrogacy | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Allowed/used | Not allowed/not used | Not mentioned | Bans traditional surrogacy | Bans altruistic surrogacy | Bans commercial surrogacy | Bans brokers | Contracts unenforceable | Case by case approval |
| Argentina | | X | | | | | | | X |
| Australia | X | | | | | X | | | |
| Belgium | | | X | | | | | | |
| Brazil | X | | | | | | | | |
| Canada | X/X | | | | | | X | | |
| Chile | | | X | | | | | | |
| Colombia | /X | | | | | | | | |
| France | | X | | X | X | X | | | |
| Germany | | X | | | | | X | | |
| Greece | X/X | | | | | X | | | |
| Hong Kong | X/? | | | | | | X | X | |
| India | X/X | | | | | | | | |
| Israel | X/X | | | | X | | | | X |
| Italy | | X | | X | X | X | | | |
| Japan | | X | | | | | | | |
| Jordan | | /X | | | | | | | |
| Mexico | | | X | | | | | | |
| New Zealand | X/X | | | | | X | X | X | |
| Norway | | X | | | | | | | |
| Romania | /X | | | | | | | | |
| South Africa | X | | | | | X | | | X |
| Sweden | | X | | | | | | | |
| Switzerland | | X | | | | | | | |
| Thailand | X | | | | | | | | |
| United Kingdom | X/X | | | | | X | | X | |

Sources: American Society for Reproductive Medicine [23]; Schuz [18]; Daniels [24]; Kindregan [15]; Werb [25]; Bateman [26]; Keppler and Bokelmann [27].

laws in the surrogate's country and laws in the intended parents' country reduce the intended parents' rights. A 2008 arrangement in India left a baby girl parentless – a "surrogacy orphan." The intended parents were a couple from Japan who got divorced while the surrogate was still pregnant. As a result of the divorce, the intended mother no longer wanted any claim to the baby. The surrogate also did not want to claim the baby. While the intended father was willing to take custody of his biological daughter, Indian law does not allow single men to adopt girls, so he was denied custody rights. Also, the father could not adopt the girl under Japanese law since the baby was still considered an Indian citizen [20]. One way to prevent similar problems from arising is for nations to establish guidelines on how a couple can establish citizenship for a child born through an international surrogate. The Australian embassy in India, for example, has outlined specific steps Australian parents need to follow in order to establish citizenship for their child after he or she is born from a surrogate in India. On its website, the embassy has the necessary forms available for download and lists recommended DNA testing labs in Australia to verify the genetic ties between the intended parents and the child [21].

Despite potential legal complications, the demand for surrogacy tourism continues to increase. In India, commercial surrogacy is growing so rapidly that the Indian Council of Medical Research predicts that it will soon become a $6 billion per year industry [16]. Planet Hospital in California, just one of many medical tourism agencies, connected 25 US clients to Indian clinics in 2007 [17]. As cancer treatment continues to improve and to save the lives of more women of reproductive age, we can expect the popularity of surrogacy to increase due to the potential reduction or elimination of their ability to gestate as a result of their cancer treatment. Indeed, surrogacy offers female cancer survivors who cannot gestate the opportunity to have biological children, as long as they are able to overcome the legal barriers found in various geographic locations.

## Conclusion

Providers who are advising patients of their fertility preservation options should include surrogacy in their discussion, rather than assume that the patients will be able to become pregnant following treatment. This is especially important for patients whose cancer or cancer treatment will probably result in an inability to gestate. In addition to general information on surrogacy, providers should mention to their patients that surrogacy is not legal in all states or all countries and that they may have to resort to surrogacy tourism. Providers do not need to be familiar with surrogacy laws in their local area, but they should be able to refer patients to surrogacy resources for more information. Knowledge of the legal barriers to surrogacy may factor into patients' decisions about fertility preservation, who may decide on another fertility preservation method in order to avoid any legal obstacles. In sum, in order for cancer patients to make informed choices about fertility preservation, they should be made aware of surrogacy as an option of having biological children and the challenges that accompany this choice.

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# Chapter 11

# Adoption After Cancer: Adoption Agency Attitudes and Perspectives on the Potential to Parent Post-Cancer

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## Introduction

The relationship between adoption and cancer may seem distant. Infertility, however, is oftentimes a consequence of cancer treatment, rendering cancer survivors incapable of biological reproduction. For this reason, the growing population of cancer survivors has a distinct relationship with adoption, as it may provide their only opportunity to parent. It is estimated that 1,479,350 men and women will be diagnosed with cancer in 2009. Remarkably, the overall 5-year relative cancer survival rate for 1999–2005 was 66.1% [1]. Since both cancer incidence rates and cancer survival rates are on the rise, the growing population of cancer survivors will likely be faced with the long-term consequences of their disease treatment, including infertility.

Research regarding the potential to become an adoptive parent post-cancer is scarce. In the one existing study that examines adoption among cancer survivors, Rosen discovered that, among a convenience sample of 11 cancer organizations, 6 international adoption agencies, and 7 adoption specialists, adoption agencies identified their chief concern as the welfare of the child and demonstrated reluctance to discuss how a cancer survivor would be viewed as a potential adoptive parent [2]. Rosen concluded that cancer patients lack access to information about adoption and may face discrimination in domestic and international adoption.

In this analysis of domestic and international adoption agencies, we aim to delve further into the intersection of adoption and cancer by looking into how prospective adoptive parents who are cancer survivors navigate the adoption process and by identifying laws and legislation that may aid or hinder them in their journey to adopt a child. We also explore legislation regarding the potential to adopt for individuals with other chronic diseases and specific lifestyle circumstances to assess how cancer survivors fit within the overall adoption system. Using information gained from agency interviews as well as personal accounts of cancer survivors, we will attempt

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to determine if cancer survivors face discrimination in the adoption process and, if so, characterize their experience and the barriers they may face. Finally, we argue for equal and just treatment for cancer survivors in the adoption system.

## Adoption in the United States

In the United States, there are three kinds of domestic adoption: public agency adoptions, which are state-licensed and usually run by state or city governments; private agency adoptions, which are also state licensed and usually incorporated in a not-for-profit form and privately managed; and independent adoptions, which involve the direct placement of a child, usually with the aid of a facilitator [3]. These various types of adoption agencies all provide the link between children in need of a home and prospective adoptive parents, assessing parental capabilities as well as assisting in the legal process and court applications. All adoption agencies have requirements mandating that prospective parents meet certain criteria in order to be eligible to adopt a child. The first step in the eligibility process is usually a home study, and most states require additional background checks and probationary placement periods along with age and health requirements thereafter. Just as adoption agency structure is varied, preferences, policies, and requirements regarding prospective parents differ considerably across agency lines.

Both domestic and international adoptions are available to individuals pursuing adoption in the US, and Americans take advantage of both types. In 2000, there were 2,058,915 adopted children in the United States, or 2.5% of all children [4]. Although adoption remains relatively rare, it is still an important means to parenthood for a variety of individuals. Domestic adoption prevails as the dominant form of adoption in the US, with 87% of adopted children in the US born domestically [4]. Domestic adoption, however, has become increasingly competitive within the United States, and the difficulties surrounding the process are impacting adoption trends. In many Western, industrialized countries (including the United States), contraception, abortion, and increasing numbers of single parents raising their children have limited the number of babies available for adoption. Conversely, in poorer countries of the world, war, political turmoil, and economic circumstances lead to an opposite scenario in which there are very few prospective adopters in comparison with the vast number of children in need of a home [5]. Inter-country adoption has surfaced as a common means to parenthood for many individuals in industrialized nations, expanding options for parenthood of children from a variety of cultural and racial/ethnic backgrounds. Indeed, the United States has been a major receiving country for inter-country adoptees since World War II, and the US is characterized as the number one "receiving" country for transcontinental adoptions [6–8]. Between 1998 and 2008, the number of children adopted from other countries has increased from 15,583 to 17,438 [9]. In 2008, the largest number of international adoptions to America came from Guatemala (4,123), followed by China (3,909), Russia (1,861), Ethiopia (1,725), and South Korea (1,605) [10]. As domestic adoptions within the

US have become more competitive, international adoptions have gained prevalence in recent years, offering many individuals increasing opportunities to create their family.

## Adoption and the Law: United States

The law, both in policy and practice, shapes the meanings and definitions of adoption within the United States. The dominant legal mode for the transfer of children in the US is plenary adoption, in which children are fully transferred from one set of parents to another [7]. Since abandoning a child is considered a crime in most legal systems (although some jurisdictions permit a form of legal abandonment in which the mother remains anonymous), adoption was created as a formal process to allow parents to legally absolve themselves of responsibility for their child, transferring this responsibility instead to a willing individual or family [11]. Adoption law essentially creates a legal parent–child relationship between persons who have no biological relationship, based on the assumption that this arrangement is in the best interests of the child [12].

The "best interests of the child" standard was established in 1865 when the Massachusetts court ruled in *Curtis v. Curtis* that "adoption is not a question of mere property… the interests of the minor is the principal thing to be considered" [13]. This standard is almost universally invoked in child custody cases, and although rarely defined, is the guiding principle in determining custody between two legally recognized parents [14]. In this way, state laws and adoption agencies employ the standard to justify individual's rights to adoption, applying various interpretations of its meaning to accommodate specific individuals. The "best interests of the child" as a standard is situation-specific and, therefore, inherently ambiguous; nonetheless, it remains the guiding criterion upon which legal decisions are often made.

The vagueness of the "best interests of the child" standard is compounded in practice by the administrative structure of adoptions agencies in the US. The vast majority of non-family adoptions in the US are arranged by private, independent agencies that usually operate on a commercial or for-profit basis [13]. These independent agencies are generally lightly regulated and characterized by wide variability in terms of policies, practices, and procedures. Consequently, adoption remains a complicated construct within the legal system of the United States. In fact, there is no national legal framework governing the adoption process, with matters of law and policy determined separately by each of the 50 states and the District of Columbia [13]. A few umbrella pieces of legislation along with related judicial decisions bring a degree of national foundation for adoption in the legal realm, but statute law, policy, and practice in relation to adoption are largely determined at the state level.

As with all aspects of family law, the Constitution (particularly the 13th, 14th, and 15th Amendments), together with the Bill of Rights, has influenced the development of adoption law within the United States [13]. In the case of adoption, the

US Constitution does not provide a fundamental right to adopt, and court challenges to the constitutionality of these restrictions have not worked thus far [15]. A number of core legislative documents, however, have shaped adoption in the US, addressing various facets of the adoption process including post-legal services for birthparents, protection and services to children placed across state lines, safe havens for child abandonment, etc.[1] On an international level, documents such as the Hague Convention, the UN Declaration on Adoption and Foster Care, and the Child's Right to Grow Up in a Family: Guidelines for Practice in National and Inter-country Adoption and Foster Care, emphasize the rights of the child as a state resource and, subsequently, the state's obligation to protect this resource [16]. These aforementioned legislative pieces build a small (and vague) framework for adoption, outlining various rights for the child, biological parents, and adoptive parents, but leaving the majority of legislative governing at the hands of individual states and countries.

As adoption is the prerogative of individual states rather than the US government, each state can pick and choose what components of these legislative pieces they want to invoke into practice for their constituents, creating a vague and indeterminate state-by-state legal system for adoption. The aforementioned administrative structure of adoption agencies further exacerbates this variability in that private adoption agencies, largely unregulated at the state level, can impose their own adoption policies and procedures. In this way, there are no clear definitions of what criteria define a prospective adoptive parent as "fit" for a domestic adoption.

Individuals pursing international adoptions are burdened with another layer of inconsistent regulations: to adopt a foreign child, an individual must satisfy the laws of the sending country and United States immigration law, on top of the laws of the state where he or she lives [5]. Although the US governmental structure imposes a degree of regulation in intercountry adoption, the exchange is essentially a private legal matter between individuals looking to adopt and a foreign court operating under its respective country's laws and regulations [12]. Some countries have a more structured system, with defined bilateral treaties or various agreements designed to govern adoption between a particular sending and a particular receiving country, but most inter-country adoption remains regulated at the adoption agency level [5].

Distinct efforts have been made to safeguard inter-country adoptions, including The 1989 United Nations Convention on the Rights of the Child and the 1993 Hague Conference's Convention on Protection of Children and Cooperation in Respect to Inter-country Adoption, which state that an ethical adoption policy should privilege domestic adoption over international adoption whenever feasible within a reasonable amount of time [17]. The Hague Convention further aims to prevent the abduction, sale of, or traffic of children, working to ensure that inter-country adoption adheres to the aforementioned "best interests of the child" standard. However, the Convention only covers contracting states, with children of non-contracting

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[1] As cited, these legislative documents include The Birthplace Assistance Act, The Interstate Compact on the Protection of Children, and The Safe Haven Laws, respectively [13].

states left unprotected. As of 2008, the Convention has been ratified by 76 countries [18].

The general lack of sound policies for inter-country adoptions has translated into a largely unregulated international system that, although founded upon the "best interests of the child" standard, lacks consistency in implementation. Indeed, legislators have failed to develop systematic policies to protect children within the international adoption system, nor have they been able to put institutional mechanisms in place to guarantee protection of these children [11]. This largely unregulated system may explain why home studies performed for international adoptions are often considered less rigorous than those for domestic adoptions [12]. In this way, inter-country adoptions may appear to be a more feasible route for cancer survivors, with certain sending countries exhibiting more permissive requirements than others.

## Existing Discrimination in the Adoption Process

Per the above discussion, the adoption process is complicated and difficult to navigate even without a potentially stigmatizing medical condition. On the domestic level, states vary with regard to factors they consider as disqualifying one's ability to adopt, with home visits and individual evaluations often entailing subjective evaluations by variable adoption agency employees. While agencies generally prefer well-off married couples as adoptive parents, some states have outright bans against individuals based on specific lifestyle and/or socioeconomic characteristics.

For example, at least six states (including Florida, Mississippi, Arkansas, Utah, Nebraska, and Minnesota) explicitly restrict adoptions by gays and lesbians. Other states' legislation attaches parental rights to birth certificates and does not allow two parents of the same sex on birth certificates, thus impeding adoption by gay and lesbian couples in an indirect way [7]. At the international level, discrimination based on lifestyle and partnership preferences is prevalent and variable. Some countries allow single individuals to adopt while others require a heterosexual marriage partnership. In a notable case against France in February 2002, the European Court of Human Rights held that allowing or disallowing gay and lesbian adoption was up to individual countries [19]. Sweden, Spain, and Iceland allow adoptions by gay and lesbian couples. Conversely, gay or lesbian couples cannot adopt children from Columbia, Eritrea, Estonia, Ethiopia, Ghana, India, Kenya, Kyrgyzstan, Lesotho, Marshall Islands, Panama, Rwanda, or Togo. In this way, various lifestyle characteristics can disqualify potential adoptive parents from the adoption process, denying them the opportunity to parent.

Socioeconomic prejudice is prevalent as well. China has specific income requirements, demanding that the total value of family assets must be at least $80,000 [10]. Most domestic and international agencies simply state that prospective adoptive parents must be financially secure and prove their financial stability. By not specifically defining financial security, these agencies rely on subjective assessments by adoption agency employees, thus opening opportunities for discrimination against potential parents.

In terms of the health status of prospective adoptive parents, international agencies are explicit regarding medical disqualifiers for adoption. Individuals cannot adopt from China if they have a number of health conditions, including AIDS, severe facial deformation, and severe diseases that require long-term treatment and that may affect life expectancy (including malignant tumors). Additionally, China will not permit individuals with a BMI of 40 or more to adopt a child. Third- or fourth-stage cancers can prevent individuals from adopting from Lithuania, and persons with "various forms of cancer" cannot adopt from Moldova [10]. No countries, however, specifically mention cancer history as a disqualifier, but rather rely on ambiguous health assessments to determine that the individual is medically "fit" to take on the responsibility of an adoptive parent.

## Interpreting the Law: Adoptive Potential of Cancer Survivors

Statewide variability in adoption policy creates ambiguity in defining who is medically "fit" to serve as an adoptive parent. Individual adoption agencies are generally permitted to use their own discretion in evaluating the health status of adoptive parents, with a variety of legal documents and specific procedures commonly used to assess the health status prospective adoptive parents.

The Uniform Adoption Act (UAA) (1994) serves as the template for adoption statutes in most US states and can be introduced and passed in whole or part by each state legislature; to date, the majority of states have rejected the document. The UAA leaves the health status of prospective adoptive parents largely unaddressed: Section 2-203 contains a brief statement about the evaluation of prospective adoptive parents, stating that a pre-placement evaluation must contain information about "physical and mental health, and any history of abuse of alcohol and drugs" [20]. Interestingly, the UAA contains extensive requirements regarding health information of the individual adoptee as well as the biological parents of the adoptive child. Cancer survivors as potential adoptive parents are not addressed in this umbrella legislation, leaving the fate of these individuals as adoptive parents up to the jurisdiction of individual adoption agencies.

Related legislation on disability broadly defines cancer survivors as a protected population, stating that applicants who are disabled cannot be excluded from consideration as adoptive parents merely on the basis of their disability. Indeed, the Americans with Disabilities Act (ADA) defines a person as disabled if he or she "has survived cancer in the distant past" [21, 22]. In this way, cancer survivors should be protected in the adoption process. However, the ADA is not routinely enforced and the rights of a disabled individual pursuing adoption have been denied by the court in at least one notable case. In *Adams vs. Monroe County*, the court dismissed an action initiated by a blind woman, supporting the right of adoption and foster care agencies to take physical disability into account as a "legitimate consideration" when assessing an individual's fitness to become an adoptive or foster parent, with the caveat that the agency does not routinely exclude disabled applicants from consideration by reason of their disability [23]. In this way, although the ADA protects cancer survivors on paper, in practice the act holds little merit, with the ultimate discretion for determining parental fitness falling under the responsibility of individual adoption agencies.

As the impact of cancer history on an individual's potential to serve as an adoptive parent is largely unaddressed and unregulated at the federal and state levels, we turned to the agency-level to gauge whether individual agencies have policies or procedures in place for this unique population. We contacted both domestic and international adoption agencies to determine their perspectives and policies on the potential to parent post-cancer. While existing laws and regulations point to potential discrimination on paper, the impact of these policies in practice is unknown. Our analysis adds another layer to the examination of the potential to parent post-cancer, incorporating both adoption agency policies as well as cancer survivor experiences with the adoption process.

## Methods

A 13-item questionnaire was developed to examine existing adoption agency perspectives, policies, and procedures toward the potential to parent post-cancer. Along with basic demographic characteristics of the agencies such as location, size, and religious affiliation, the questionnaire inquired into whether adoption agencies screened potential parents based on health or lifestyle characteristics, and whether or not the agency currently had a policy in place for individuals with a cancer history. The questionnaire was approved by the Institutional Review Board (IRB) of Northwestern University. Twenty-seven agencies were contacted, representing 21 states throughout the US. All agencies were found through the Child Welfare Information Gateway: National Foster Care & Adoption Directory.[2] Private-domestic, private-inter-country, and public adoption agencies were searched for by state. All agencies were contacted via telephone. For purposes of geographic diversity, once an interview was obtained from an agency in one state, no more agencies from that state were contacted. However, if a representative from an agency returned a call and agreed to be interviewed, the interview was accepted, even if the agency was from a state that was already represented in an interview.

We spoke with a variety of agency personnel, including executive directors, directors, counselors, case workers, coordinators, social workers, family specialists, administrative assistants, and child protection specialists. Out of twenty-seven agencies, twenty three agencies self-identified as private, while four self-identified as public. Eight agencies (30%) offered domestic adoptions only, three agencies

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[2] The Child Welfare Information Gateway: National Foster Care & Adoption Directory can be found online at: http://www.childwelfare.gov/nfcad/

(11%) offered international adoptions only, and sixteen agencies (59%) offered both domestic and international adoptions. The international agencies adopted from a combined 20 different countries across the globe. Financially, the average cost for agencies offering domestic adoption only was lowest ($16,062.50), compared with agencies offering international adoption only ($19,722.30) and agencies offering both domestic and international adoptions ($21,058.00). On average, the agencies completed 93 adoptions per year. Five agencies, or 27% of the agencies contacted, indicated a religious affiliation. Of those who self-identified as religiously affiliated, three agencies identified as Christian, one agency identified as Catholic, and one agency identified as mainline/liberal protestant. Although the sample is relatively small, we aimed for diversity in size, geography, and religious affiliation.

Additionally, we joined an informal online support group for cancer survivors who are interested in or have pursued adoption. Our membership in this group and access to individual experiences was approved by the IRB of Northwestern University. We used publicly available information about individual experiences with the adoption process to augment our agency-level analysis.

## Results

Adoption agencies were generally very vague in describing how cancer survivors would navigate the adoption process. They varied in terms of the required components of a medical status screening. Namely, four agencies required a physical only to determine the health status of the prospective parent. Three agencies required that a physician fill out an agency-specific medical form, and four agencies required both a physical and an agency-specific medical form. Seven agencies required a physical along with a doctor's attestation of health and seven agencies required a physician note only. Finally, one agency explained that they complete the medical screening independently, and one agency required an entire medical history of an individual. The medical screening requirements by agency are summarized below in Table 11.1.

**Table 11.1** Medical screening requirements by agency

| Medical screening requirements | |
|---|---|
| Physical only | 4 |
| Agency-specific medical form to be filled out by physician | 3 |
| Both physical and agency-specific medical form to be filled out by physician | 4 |
| Physical along with doctor's attestation of health | 7 |
| Physician note only | 7 |
| Placement agency completes medical screening independently | 1 |
| Entire medical history | 1 |

In terms of the relative importance of past versus current medical status of prospective adoptive parents, 15 agencies responded that they screened for both current and past medical status, 8 agencies indicated they only screened for current medical status, and 1 agency said they screened for neither.[3] Of the agencies that screened potential parents on their past medical history, the agencies screened an average of 17.28 years into the past.

We asked agencies whether there were any specific medical conditions that would prevent potential parents from adopting in an attempt to draw parallels between cancer and other chronic diseases and lifestyle characteristics that may exclude individuals from adoption. Eighteen agencies responded that there were no medical conditions that would disqualify potential adoptive parents while seven agencies admitted that a number of specific medical conditions would prevent individuals from adoption within their agency, citing a variety of illnesses and medical conditions that included contractible diseases, AIDS, and terminal illnesses. A complete list of the medical conditions that were mentioned is included below in Table 11.2.

**Table 11.2** Specific medical conditions that would bar potential parents from adoption, as cited by specific agencies

| Specific medical condition as defined by agency |
|---|
| Contractible diseases |
| AIDS |
| Active, life-threatening diseases |
| Anti-depressants |
| Terminal illnesses that shorten lifespan (2) |
| Conditions that require a large amount of narcotics that render individual unconscious; substance addiction; severe mental conditions like schizophrenia |

In terms of discrimination based on lifestyle preferences, 11 agencies indicated that specific lifestyle characteristics would prohibit individuals from adopting with their agency. These responses were related to marital status (5), sexuality (3), drug/alcohol abuse (2), and religion (1). Specifically, three agencies identified that they would not allow unmarried individuals to adopt, one agency indicated that an individual who is separated would not be allowed to adopt (they must be formally divorced), and one agency would not allow single men to adopt.

Cancer history was not specifically addressed by the majority of the adoption agencies; only one agency indicated that they have a policy in place for prospective adoptive parents with a history of cancer, and their self-described policy was rather ambiguous. The agency asserted that cancer history would be addressed during the individual home study, and the ability for the individual to adopt would depend upon how long the survivor has been in remission. The other 26 agencies did not identify a policy in place for cancer survivors, although two mentioned caveats, with one stating that an individual with a cancer history must have a reasonable life

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[3] Additionally, two agencies abstained from answering this question.

expectancy and another requiring a doctor's affirmation health. All agencies were also asked whether the number of disease-free years would be relevant in assessing a prospective adoptive parent with a cancer history. Seven agencies (26%) indicated that the number of disease-free years would be relevant, while nine agencies (33%) claimed that this information would not be important, with an additional four agencies not aware of the importance of this information and one agency claiming that the importance of the number of disease-free years would be assessed in the doctor's note.

On a related note, agencies were queried on whether they have a policy in place for prospective adoptive parents who are HIV positive. Two agencies responded positively, with one agency noting that HIV positive individuals (as determined through doctor's physical) would be disqualified from adoption and the other citing their resident state's law regarding the right to adopt for HIV positive individuals.[4] The remaining 25 agencies indicated that they do not currently have a policy in place for prospective parents who are HIV positive.

When asked what percentage of adoptive parents receiving children from their agency were cancer survivors, agency personnel seemed largely unaware. Individual responses are included below, with the majority of agencies stating that less than 2% of adoptive parents using their agency have a history of cancer (Table 11.3).

**Table 11.3** Percentage of adoptive parents who are cancer survivors by agency

| Percentage | Number of adoption agencies (n = 27) |
|---|---|
| Zero | 2 |
| <1% | 6 |
| 1–2% | 2 |
| 2% | 3 |
| 3–5% | 1 |
| 4% | 1 |
| <5% | 2 |
| <10% | 1 |
| 10% | 1 |
| Maybe 10% | 1 |
| Very low/very small | 4 |
| Don't know | 3 |

As far as protocols for current cancer patients, three agencies indicated they have a policy in place, while 24 agencies indicated that they do not. The three agencies' policies for current cancer patients include a requirement for a doctor's statement that the individual's lifespan would not be shortened, a conversation with the patient's primary doctor and oncologist, and a stipulation that the patient suspends the adoption process until treatment is complete.

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[4] Notably, extensive research into state laws regarding the potential to serve as an adoptive parent for HIV positive individuals yielded no results. While this may indicate inadequate research, it may also reflect misconceptions among adoption agency employees as to the source of their own policies.

In an attempt to gauge how these adoption agencies wanted to be perceived regarding their positions on cancer survivors as adoptive parents, we borrowed a question from Rosen's initial study, asking all agencies whether they would like to be known as a cancer friendly agency. Nineteen agencies (70%) responded yes, four (15%) responded no, three (11%) were unsure, and one agency (4%) did not respond. On a related note, 22 agencies agreed that cancer survivors should reveal their cancer history, 3 agencies stated that a cancer survivor should not reveal his/her history, and 2 agencies stated that this decision is up to the individual applying for adoption.

## Discussion

Various types of discrimination are apparent in the adoption process, with certain medical conditions and lifestyle characteristics disqualifying individuals (as evidenced by both legal proceedings and agency policies) from adopting children in different states and from agencies throughout the United States and abroad. As earlier described, there are no specific legislative documents in the United States that categorically prohibit cancer survivors from serving as adoptive parents to a child in need. This fluctuating prejudice against cancer survivors speaks to the informal process in which adoption agencies can essentially pick and choose who they accept as reasonable adoptive parents. The inherent structure of the adoption process facilitates this complication. Adoption in the US operates with the same free-market ethos as other commodity exchanges, with adoption placements not subject to a tight regulatory system; consequently, the exchange of children operates through a mixture of official law and its interpretation, discussion, and rights claims [7, 13]. An individual with a clean medical history competing against a cancer survivor to adopt a child would arguably receive preferential treatment, based both on the aforementioned "best interests of the child" standard as well as the relative freedom adoption agencies have in choosing adoptive parents. In this way, although cancer survivors are not specifically disfavored against in writing, they are subject to the market exchange ethos of the adoption process, and therefore, subject to open and consistent prejudice in trying to adopt a child.

Although existing legislative documents such as the Americans with Disabilities Act (ADA) protect cancer survivors' rights to adopt a child, these protections are largely inconsequential in practice. As evidenced by the court decision to rule in favor of the adoption agency to discriminate against the blind woman trying to adopt, the ADA often provides little protection in application [23]. Cancer survivors, like many other marginalized populations, are left to fend for themselves against discrimination in the adoption process, with no official or reliable legal protections granted to them. While the legal analysis points to the protections lacking for cancer survivors, the adoption agency analysis highlights the various ways in which cancer survivors may face discrimination.

As previously described, the network of adoption agencies working with potential parents in the US is characterized by fundamental variability and ambiguity. In terms of the health status of prospective parents, all agencies required some form of medical screening, ranging from physicals to agency-specific medical forms to doctor's attestations of health to entire medical histories. These stipulations, required either individually or in combination, are also innately subjective. Individual physicians are allowed to determine what kind of information is relevant to an individual's potential to parent, with doctors using their discretion to determine medical fitness to parent. Even when agencies do require specific medical forms, these vary significantly from one agency to the next. We were granted access to two different medical forms required by agencies involved in our study. The first form inquired about general health status including allergies, obesity, and heart disease; the only place where cancer could feasibly be addressed was in the section asking about past hospitalizations and history of previous diseases. But, as with doctor's notes, all information on the specified form is subject to physician interpretation. The second medical form was far less comprehensive than the first, with cancer history likely addressed in a section asking about the patient's medical history as well as the following question (as presented to the physician): "Is this patient's life expectancy normal?" The remaining agency-specific medical forms that we were not granted access to view presumably cover the same broad range of topics, probing into a patient's medical history, but not directly asking for cancer history. Therefore, it is clear that among the agencies interviewed, cancer history in and of itself is not a distinct component in the evaluation of an individual's medical history.

Specific medical conditions that disqualify an individual from adoption, as noted by adoption agency personnel, include a variety of health conditions such as AIDS, active life-threatening diseases, and terminal illnesses expected to shorten lifespan (See Table 11.2). Cancer history could arguably be implicated in the "terminal illnesses expected to shorten lifespan" category, although this claim could be refuted by the argument that in the case of many cancer survivors, the illness is clearly not terminal, as they are currently alive and disease-free. The minority of survivors who do relapse, however, could be characterized as having a "terminal illness," depending upon their specific diagnosis.

The apparent lifestyle discrimination, as supported by courts both domestically and internationally, was supported in our analysis of individual adoption agencies. Agency personnel identified marital status, sexuality, drug/alcohol abuse, and religion as potential disqualifiers for individuals using their agency. Interestingly, these forms of discrimination are both transparent and accepted, pointing once again to the negative implications for marginalized populations as generated by the free market system of adoption in the US.

Explicit prejudice against cancer survivors was less obvious in this sample: only one agency indicated that they have a policy in place for cancer survivors, stating that the individual's health would be addressed in the home study and their eligibility to adopt a child would depend upon how long the survivor had been in remission. Interestingly, the type of cancer, stage at diagnosis, and other relevant medical conditions were not cited as necessary information in interpreting an individual's cancer history. Instead, in this instance, the number of disease-free years truly determined a cancer survivor's potential to adopt. Further, a greater number of agencies (9) claimed that the number of cancer-free years would not be important in determining parental eligibility than the number of agencies that claimed that these numbers would be important (7). Adoption agencies do not have specific policies that protect or prohibit cancer survivors from adopting, leaving cancer survivors vulnerable to potential informal discrimination. Although harder to prove, this informal discrimination is supported by the general lack of knowledge about cancer survivorship made apparent during conversations with agency personnel.

For example, when asked what percentage of adoptive parents who have successfully adopted a child from their agency are cancer survivors, agency employees were relatively unaware but indicated that it was a very small amount. The fact that agencies are not acutely aware of cancer survivors within their system could be due to the fact that few cancer survivors have approached their agency, or, conversely, that cancer survivors have not made it past the medical screening portion of the adoption process. Indeed, during an interview with one of the agencies, we were provided with anecdotal evidence that there had been a case where a couple affected by cancer had difficulty adopting from a competitor agency. This was the only specific case that was referenced in regard to cancer survivors; no cases of successful adoption by cancer survivors were presented to the researchers by adoption agency personnel.

This general lack of information from adoption agency personnel is in sharp contrast with a general desire (on behalf of the adoption agencies) to be known as a cancer-friendly agencies. Although these agencies would like to be known as cancer-friendly, they are not explicit in their policies regarding adoption by cancer survivors, thus effectively permitting discrimination against cancer survivors, a bias that is further facilitated by the variability and subjectivity in their assessments of parental fitness. This discrepancy may stem from individual agencies wanting to be perceived positively by the public and to shy away from claims of prejudice against any marginalized group. We are not arguing that all adoption agencies discriminate specifically against cancer survivors, but rather that the current adoption system permits informal prejudice in practice that likely varies from one agency to the next. In this way, the inherent subjectivity in screening for prospective adoptive parents likely means that cancer survivors seeking adoption may be successful in one agency but unsuccessful in another.

Birth mothers can also play a role in discriminating among potential adoptive parents. In the majority of independent placements, birth mothers determine the ultimate suitability of adopters, and therefore, can openly disfavor against cancer survivors. The right of a birth mother to place her child for adoption with whomsoever she chooses, or to authorize another person to do so on her behalf, has been embodied in the laws of all but four states[5] [20]. The exact influence of a birth mother's preference, however, is hard to characterize on a broad level, as birth

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[5] Colorado, Connecticut, Delaware, and Massachusetts.

mothers often relinquish their rights to private agencies in the context of private adoptions. In the case of public adoptions, the rights of the birth parents are often judicially terminated, with government agencies thus shouldering the responsibility of placement decision making. Based on the form of adoption they use, therefore, birth parents can freely exercise their own discretion in choosing adoptive parents, adding another potential opportunity for discrimination against cancer survivors.

## Expanding the Discussion: The Experience of Potential Adoptive Parents

While agency interviews unveiled informal policies, perspectives, and general practices, individual accounts from prospective adoption parents added another layer of support to this analysis. In establishing contact with an informal online support group for cancer survivors considering adoption, we gathered some anecdotal evidence on actual experiences with the adoption process. A couple with a cancer history shared their experience with adoption, indicating that they had tried dual approaches in informing agencies of their cancer history – both upfront honesty as well as vague avoidance of the subject – with both approaches ultimately unsuccessful. Another cancer survivor passed along recommendations that agencies willing to work with single parents and same-gendered couples seem more open to accepting cancer survivors as adoptive parents, speaking once again to variable discrimination as presented by some agencies but not others.

A breast cancer survivor described her multiple attempts at adoption, first trying an open, honest approach about her cancer history, only to be turned down in the early stages, and trying again with a more vague approach, but denied once her doctor mentioned her cancer history. In the words of the survivor herself, cancer survivors are often lost in the adoption process, lacking practical information about how to share their cancer history with an adoption agency and subject to intense emotional distress as a result of their medical history.

> I have found the whole experience to be an emotional roller coaster that mostly has lows. I feel like I am being discriminated against because of my health. I haven’t made it very far in the adoption process but we are still trying [. . . ] I wish there was a step by step guide about how to adopt with cancer. It’s like a big black hole that you are blindly trying to crawl out of. Sometimes you get glimpses of light, but most of the time you are in total darkness.

The real experience of cancer survivors in the adoption process is not described as a pleasant one, but rather a discouraging process in which individuals feel hindered by their health history. Cancer survivors who have attempted adoption express frustration with the process and the intra-country inconsistencies and inter-agency variations regarding their potential to parent. As described by a female cancer survivor who has been waiting on an international adoption for over a year, agencies themselves are often ambiguous about their own rules, and discrimination against cancer survivors is open and apparent:

> The other thing that bothered us was the variety of answers we heard about a particular country's rules regarding international adoption and cancer – some agencies said the rules were the country's, some said the were agency rules, and in some cases it wasn't clear [. . .] Someone told me recently that it's illegal for agencies to discriminate against a family based on a cancer diagnosis. If that is true, there is a lot to be done in that area particularly with agencies that deal with international adoption, because there is whole sale discrimination and misinformation out there. It's also nearly impossible to get a good idea of what your options (internationally) are without a lot of research, and a lot of guesswork based on many, many phone calls. It would be helpful if agencies would provide clear information about their program's cancer rules or at least have a written policy about how they will handle survivors of cancer.

Not only are cancer survivors at a distinct disadvantage in the adoption process, but they are also lacking information about their rights to adoption. Adoption agency policies are difficult to locate and interpret, leaving cancer patients deprived of the information and facts they need to most easily pursue an adoption.

Adoption after cancer, however, is a possibility, as evidenced by an account of a successful adoption by a breast cancer survivor. Just 2 years after her diagnosis, a woman and her husband adopted a14-month-old through an international agency. Although they were eventually able to adopt, the road to their adoption was not straightforward. The woman and her husband attempted adoption through several agencies in the same foreign country, with a number of agencies prohibiting her from adoption based on her medical history. The agencies that rejected their request cited an alleged country-wide cancer policy, even though the couple eventually adopted a child from this same country.

> The only difficulty and frustration that I experienced as a cancer survivor was being rejected by some adoption agencies based on their own cancer history policy, which claimed to be [the country's] policy

As seen in our own analysis, adoption agency employees are often unaware of their own policies and procedures regarding the health of prospective parents – this general lack of information permits informal prejudice against cancer survivors in the adoption process.

## Defining the Discrimination

In sum, there is evidence that cancer survivors face de facto discrimination when navigating the adoption process, discrimination that is not present systemically but rather in isolated agency cases. Inherent variability in the adoption system, state policies, and individual medical assessments means that this discrimination can surface in various forms at various points in the process. One survivor may be denied outright, while another may face exclusion during the home study and another during a doctor's examination, while a fourth may get a lucky break and successfully adopt a child.

This form of discrimination is, by definition, difficult to define, and even harder to prove. However, the information gathered from the legal analysis, combined with the adoption agency surveys and personal accounts all speak to the potential for discrimination against and the lack of protection for cancer survivors as adoptive parents. Cancer survivors are not a protected population nor are there any specific policies that prevent them from adopting, but the current interagency variability contributes to discrimination in practice. Informal, inconsistent discrimination against cancer survivors is manifested on a case-by-case basis during the adoption process.

A number of limitations may have influenced the findings from the adoption agency analysis. The relatively small sample size ($n = 27$) may make it difficult to draw significant conclusions from the data. Our sample was also largely composed of private agencies ($n = 23$), with only four agencies representing the public sector. Finally, religious affiliation may understandably impact adoption agency policies and procedures; including a more religiously diverse sample could have strengthened our analysis. There was also wide variety in the knowledge, expertise, training, and experience of the agency personnel whom we interviewed. Because we interviewed anyone who was willing to speak with us, our interviewees included a diverse group of employees. The position and perspectives of the individuals whom we spoke with influenced their responses, which may have biased our results. Finally, this study only takes into account the perspectives of the adoption agencies and a handful of adoptive parents, but no birth parents. This analysis points to the need for a larger, more extensive, and detailed study of cancer survivors in the adoption system to include an emphasis on individual experiences and the perspectives and preferences of birth parents. Despite these limitations, we are confident that our analysis provides a novel description of the adoption process, underscoring the difficulties faced by cancer survivors pursuing adoption.

## Conclusions

De facto discrimination pervades the adoption process for cancer survivors, manifesting itself at various points of the adoption process and through various mechanisms. Although documents and legal protections (such as the ADA) define cancer survivors as a protected class and thus prevent against discrimination in the adoption system on paper, these protections are ineffective in practice. As the majority of adoption agencies do not have specific policies in place to define how they handle prospective adoptive parents with a cancer history, cancer survivors experience varying forms of informal discrimination, as evidenced by individual accounts and narratives as well as adoption agency interviews.

Arguing for a more defined policy for prospective adoptive parents who are cancer patients is a double-edged sword. While this call could bring protection to individuals and secure their right to adopt, it could also result in blanket discrimination that prevents individuals from adoption. As such, the variability of the status quo permits prospective parents to “shop around,” just as it permits agencies to pick and choose (even if arbitrarily) adoptive parents. Thus, it is difficult to gauge which system would provide the most protection for cancer patients, as the current interagency variability may allow persistent cancer survivors to eventually locate an agency who will approve their request for a child. As previously demonstrated, protective documents and policies do not ensure safeguarding in practice. Within the current adoption system, cancer survivors are recommended to adequately research a multitude of adoption agencies in their effort, and to not give up after the first sign of dissent, as the variability in policies and practice may eventually prove to their benefit.

The implications of this de facto discrimination in the adoption system carry over into cancer patient clinical care. Since adoption is not a guaranteed option for cancer survivors, individuals facing a diagnosis may be urged to protect their biological capacity to reproduce in case adoption proves impossible. In this way, fertility preservation technologies may provide cancer patients with a back-up option in the face of uncertain adoption outcomes, enhancing the potential to parent post-cancer.

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# Part III

# Clinical and Theoretical Ethics

# Chapter 12
# Ovarian Tissue Cryopreservation and Bioethical Discourse

**Cristina L.H. Traina**

## Introduction

As the chapters in this volume demonstrate, like other nascent medical technologies ovarian tissue cryopreservation (OTC) raises no earth-shatteringly new moral questions. Rather, it poses old moral questions in new ways, thus shedding light not only on our old answers but also on our old methods of reaching them. My task here is to point out the ways in which OTC forces us to embrace important changes of emphasis in bioethics discourse around reproduction, changes that were already burgeoning and are now being reinforced by the unequivocal demands of this particular technology. All but the last of these is specifically tied to discussions that have preoccupied philosophical and religious feminism; the last, as a logical consequence of the first four, connects indirectly.

Jacci Stoyle's incisive critique of Christian moral reflection on in vitro fertilization (IVF) provides a helpful foil [1]. Why, she asks, despite the extraordinary risk and discomfort that *women* must undergo in order to receive IVF, does the literature so thoroughly elide women (except as containers), focus so heavily on the moral status of the *embryo*, and emphasize men's anxiety over infertility and embarrassment with treatment procedures? Given that the whole purpose of IVF is to create an expanded web of familial relationships, why does the literature focus on conflicts of individual rights? I argue that the ethics of OTC helpfully reframe the reproductive technologies debate, moving us out of the logical ruts in which the ethics of reproductive technology often seems to be mired, despite the presence of alternative models.

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## Medical Solutions to Social Problems

For feminists, the observation that medical procedures are solutions to social problems is usually pejorative. In this volume, Carolyn McLeod has raised the question of whether socially mandatory motherhood might not put inappropriate pressure on female cancer patients to undergo the expense and risk of preserving ovarian tissue, or on parents to put their young, ill daughters through additional surgery [2]; Adrienne Asch has noted that this possible technical "fix" discourages self-critical examination of our socially formed desires for mother- (and grandparent-) hood [3]. With colleagues, I have raised the same question about reproductive technologies generally in my own work: especially outside the first world, does reproductive technology solve a medical problem, or does it merely overcome the shame and resultant social and economic marginalization that result from unquestioned, legally enforced patriarchalism [4]? And yet Angel Petropanagos shows that in important ways ovary cryopreservation is morally identical whether one undertakes it because of the likely sterilizing effects of cancer therapy or whether one simply anticipates delayed childbearing. In the absence of a partner or a steady job, the latter may be as involuntary as the former [5].

In a very real sense, Petrapanagos's reasoning reminds us that *all* medical procedures solve social problems. This observation is a cornerstone of Anglo-American feminism, which makes the same argument about abortion, which it embraces, and breast augmentation, which it generally decries. But this truth extends far beyond such significant surgeries to much less controversial therapies. I am frequently conscious that the primary effect of synthetic thyroid hormone, taken by millions, is relational, familial, and social. With it I can be more productive, energetic, and generous. Certainly it addresses an organic problem, but that problem came to my attention only because of its social consequences. In keeping with feminist emphasis on relationality, we should be consistent: in fact, the overriding purpose of most medical interventions *is* to improve human relationship and interaction. Condemning the use of medicine to solve social problems is hypocritical; we should instead ask whether medical intervention is the *best* way to solve a particular social problem – in this case, the perceived disvalue of future infertility. Perhaps, one could argue, thyroid hormone replacement is defensible because it supports communal interaction, productivity, happiness, and physical health in all social circumstances, whereas OTC should be subjected to further critical analysis because it responds to a social judgment, perhaps reinforced subtly by relational or economic penalties, that non-mothers cannot be "real" women rather than to a general, universal prerequisite for an engaged life. But we must consciously make these kinds of distinctions, not breezily condemn or champion "the use of medical intervention to solve social problems."

## Making Room for a Language of Care

Feminism's political goals wed it necessarily to the language of legal rights. As reproductive justice, these rights include freedom both from coerced pregnancy and motherhood and from coerced infertility and child removal. They also include access to the resources necessary to raise children well [6, 7, p. 42]. Quite simply, women have the legal rights to decide whether to be mothers and to parent the children they have, rights that in turn produce an entitlement to basic social and economic goods.

Although legal rights comprise a necessary baseline for social justice, they are not sufficient for moral discourse. Partly because of bioethics' practical preoccupation with the legal implications of human subjects review, however, bioethicists do at times speak as if the language of legal rights exhausted the responsibilities and insights of bioethics. For example, Stoyle notes that discussions of IVF tend to focus upon generic rights and conflicts of rights: the rights of the embryo, the rights of the parents over the process, the rights of the parents over gametes or embryos, and the rights to funded IVF cycles [1, p. 214]. These approaches minimize the ethical concern for care that ought to drive clinical practise, a concern that comprehends the particulars of each patient's medical and social situation and strives for her holistic flourishing.

In the chapters in this volume, on the other hand, such reflection tends to be more conditional, interrogative, and open-ended. Will an additional invasive medical procedure be an unwelcome stress? Is the patient able to participate in the decision, and if the patient is a child, how heavily should her parents' desires be weighed in a given situation? How likely is it that the patient will be able to become a parent later? Is expense a factor in the decision whether to freeze ova or ovarian tissue, and if it is, should it be [8]? In reproductive ethics generally, once the basic demands of legal rights have been satisfied, these essential questions take center stage. They may reveal patterns that have important, broad implications (for instance, expense as a barrier to fertility preservation, or parents' strong desires for grandchildren); as Joan Tronto argued years ago, these kinds of care considerations too, not just basic rights claims, should shape the policies we create to guarantee justice [9]. But this insight should not obscure the methodological point: these considerations arise not from abstract theorizing about rights but from care for particular patients in their specific circumstances.

Beyond this observation, however, the authors in this volume also encourage us to use care considerations to refine our rights language self-critically. Certainly we must defend basic reproductive justice for all women, but this may not imply that society absolutely owes every woman the right to become a genetic, gestational, and social mother regardless of her circumstances. As part of our mandate to care, we must also protect vulnerable children's welfare, make important decisions about limited medical resources, and realize that 100% fertility is an unrealistic goal. OTC spotlights these important questions. Distinctions must be made between the legal right to exercise fertility and the moral wisdom – based in care – of doing so. For instance, Clarisa Gracia hints that some women should probably opt to forego motherhood because of precarious health, even if conception and gestation are possible [10]. Asch reminds us that not merely fertility patients, but all adults ought to consider carefully whether they are up to the task of parenting before they undertake it [3]. These are bioethical questions, even if they are not questions that clinicians should have the right to answer for their patients.

## Replacing Present Operations with Future Vocations

As Stoyle shows, the ethics of assisted reproduction is too often misconstrued as the ethics of the discrete acts or operations meant to achieve conception. The gametes' origins, the methods of fertilization and implantation, and the fate of unused embryos and gametes (not only their preservation or disposal but also rights over them) crowd our moral view. Questions of vocation – self-consciously adopted life plans that shape subsequent moral decisions – tend to appear only in religious discussions of the purposes of marriage, and even here they prove Stoyle's point. For example, influential representatives of traditions like Roman Catholicism, Orthodox Judaism, Sunni Islam, and Eastern Orthodoxy tend to qualify their argument that marriage should include procreation precisely at the point where they believe that the embryo's integrity is compromised, either medically or socially [4, 11].

By contrast, oncofertility ethics is driven almost entirely by questions about future vocational options: all things being equal, should we choose treatment options that not only are more likely than others to preserve future fertility (a common consideration), but do so by actually removing the gametes from the path of radiation and chemotherapy drugs? In other words, should we choose treatment options that preserve a girl's or woman's future vocational decision whether to become a mother in what we think of as an ordinary way? Should we treat her cancer in such a way as to remove as many contingencies and roadblocks as possible from her future decision whether to become a parent?

Importantly, this is not a matter of *guaranteeing* the future possibility of motherhood through vaginal intercourse. It is not yet clear that ovarian tissue can produce live births with routine success, and of course nothing can guarantee against male infertility, fallopian tube defects, and other obstacles to fertility unrelated to ova. Even more importantly, it is also not a matter of preserving the capacity for motherhood, period. Lack of gametes does not preclude social motherhood for anyone; "other mothering" is open to all. It also does not preclude legal motherhood, as women of adequate means can certainly adopt children.[1] It does not even preclude gestational motherhood, as women (again, of adequate means) can certainly conceive with donor eggs. Lack of viable ova precludes only the possibility of genetic motherhood (now the overriding Western definition of kinship [12, 13]) and the possibility of conceiving through heterosexual intercourse (which is less invasive than assisted reproduction, more acceptable to many religious groups, but problematic for lesbians and some single heterosexual women).

Thus, highlighting the connection between OTC and future vocational choices returns to center stage moral questions that are sometimes pushed to the wings in discussions of other assisted reproductive technologies. Cancer treatment by itself is no obstacle to a future vocational decision for maternity, even when it causes sterility. Far more important are the social and economic capital that allow even

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[1] Adoption is not a substitute for gestational motherhood in Islamic cultures or in some Hindu communities [4].

women lacking ova freely to choose *how* to become mothers and allow even fully fertile women truly to choose *whether* to do so. OTC questions force us back to the larger picture: overcoming poverty, improving access to basic medical care, and eroding cultures of compulsory or unjustly forbidden motherhood where they exist. OTC turns out not to be about preserving the possibility of motherhood at all but simply about increasing the number of paths to motherhood from which a woman might later choose.

## Adaptation or Transformation?

Because of its focus on women's welfare, feminism naturally produces a double emphasis: critique and long-term transformation of the social circumstances that harm women and immediate, practical adaptations and services that will allow women to flourish within the constraints of the unjust society in which they still live. This double critique necessitates self-criticism: by supporting adaptations, are we inadvertently legitimizing the unjust circumstances the adaptations mitigate? By fighting for change, are we inadvertently neglecting women's current urgent needs?

As Goold and Savalescu have argued in the case of elective freezing of eggs [14], preservation of ovarian tissue need not be limited to cases of possible cancer therapy-induced infertility. Women could use it widely to hedge bets against their future declining egg quality. By playing into both a culture of compulsory motherhood and a culture of work that punishes childbearing in early adulthood, the practise could distract us from the social pressures on women's reproduction by permitting us to resolve them on a personal level (finances and technology permitting). This phenomenon distracts ethics too, focusing attention on procedures, protocols, and even access rather than on the larger social problems that are at least partly responsible for creating the perceived need for fertility therapy. Yet by making delayed childbearing possible without use of donor eggs, these practises also have the potential to transform society's double standard on "mature" genetic parenting: acceptable and even approved for "settled," wiser, older men, and monstrous and unnatural for older women [14].

Goold and Savalescu's argument points toward a both/and approach: meet current needs while reflecting morally on possible socially transformative consequences and seeking long-term justice. Commitment to the kinds of social change that remove obstacles to women's reproductive freedom should not preclude "allowing access to technological advances" that can help them plan motherhood more freely while the obstacles are still in place [14, p. 50]. We just need to be savvy about the likely results.

We also need to be savvy about the distinctions. Even if freezing eggs or tissue is in some ways morally equivalent whether it is done as insurance against future declining egg quality or against likely therapy-induced infertility, are the two procedures morally equivalent in all ways? For instance, OTC requires us to contemplate parents giving permission for their minor daughter's ovarian tissue to be surgically removed and stored before she undergoes chemotherapy. Suppose a child who is cancer-free is scheduled to undergo another procedure under general anesthesia. Should her parents be able to request that ovarian tissue be removed and stored as a safeguard against her possible future illness or infertility? Or suppose that the child is perfectly healthy, but the parents want to elect the surgery for her, much as one might (expensively, laboriously, and uncomfortably) correct a child's bite so that her molars will be likely to last longer into her adulthood? This leads us to a further set of questions.

## The Patient's "Best Interest"

Narrowing the frame of reference to the patient's best interest is another favorite method of simplifying the ethical discussion of assisted reproduction. This strategy has its place in certain circumstances. In the case of OTC, adults can presumably make decisions about their own fertility and live with the consequences of these choices. Patients who stored ovarian tissue could choose to have it destroyed at a certain point; some women who elected not to store tissue would conceive anyway, and others who wished to be parents would find other ways to mother. In OTC the "best interest" of the patient comes into play primarily for children, whose reproductive periods are farther off and whose lives may take unpredictable turns in the intervening years. Here, the calculus is harder [8, 15, 16].

From a feminist perspective, the question of the patient's best interest raises two concerns: the patient's current and future welfare (not just protection from harm, but holistic flourishing) and her agency in later life-shaping decisions. From both perspectives preserving ovarian tissue seems acceptable *if* there is a good reason to believe the child's fertility will be destroyed. If the surgery and storage are not terribly burdensome or expensive, they leave a girl the option to decide *in the future* whether she wishes to undertake further surgery or treatments to attempt genetic motherhood. That is, without jeopardizing her current or future health, they increase her options around an issue that is deeply freighted with social and psychological meaning without prejudicing her toward motherhood.[2] But subjecting a child to every possible preventative therapy or intrusion in order to guard against unpredictable future mishaps would not be in her best interests.

Two further worries seem overblown. The first is that parents should not make decisions of such great significance to their children's bodily and social futures alone, and the second is that the OTC discussion burdens both parents and children inappropriately. Both demand sensitivity, but neither takes on such unusual significance that it should forbid the therapy altogether.

First, parents make life-altering choices for – and by degrees, as it becomes appropriate, with – their children all the time. Some of these decisions momentously,

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[2] It can be argued that the existence of the ovaries could pressure a woman to use them; this is true, however, of the "biological clock" for fertile women. In both cases biology and social values combine to create pressures that exist independently of OTC.

even permanently and irrevocably, affect their children's futures. These decisions, both medical and social, are not trivial. One controversial example is the decision whether to create more socially acceptable genitalia surgically for intersex infants. Yet this example is contentious precisely because intersex surgery *narrows* a child's future possibilities before the evidence of puberty indicates the direction the child's body might take on its own. Preserving ovarian tissue, on the other hand, *preserves* or *expands* the future possibilities open to the future cancer survivor.

Second, changing contexts will mute the moral relevance of some pressing clinical ethics concerns. For instance, the psychological impact argument is a moving target. Questions about organ donation used to be considered high-stakes, invasive, and problematic intrusions into a family's already-complex grief. Now they are so commonplace that, in some states, they are a routine part of the driver's license application process. Similarly, some current writing on OTC seems to assume that the question of fertility preservation will broadside vulnerable parents (and patients) unfairly [17, pp. e1464–1465]. However, if queries about fertility preservation were a widely accepted, routine oncological practice [16, p. 27] – so widely accepted that parents would be as ready to face this question as they are now prepared to face the question "radiation, chemotherapy, or both?" – this psychological barrier would disintegrate. In both these cases, expanding the question beyond one particular child and one particular decision provides historical perspective that lessens the urgency of the question.

Feminist discourse drives us toward the languages of expansive choice and flourishing, including relational and social flourishing. Especially in the case of child cancer patients, effective therapy should preserve as broad a spectrum of possibilities for the child's own future self-realization-in-community as it can without imposing significant suffering or expense. But this dedication to preserving possibilities – in this case, of genetic motherhood – should not subtly, unquestioningly value genetic motherhood over other possibilities. Critique of cultural values and of justice priorities for medicine also comes into play.

Thus the feminist analyses that OTC encourage press us to expand our questioning about fertility therapies beyond procedures and personal health to the social, relational, and cultural contexts of fertility. In the case of OTC, which raises few new ethical or procedural questions, the new therapy, if perfected, certainly is salutary: it increases the *options* women have for mothering. But we should probably not go so far as to claim that it is a matter of *reproductive justice,* as infertility caused by cancer or menopause is not unjust unless the cancer or menopause is the direct result of unjust human influences like environmental contamination. The simple inability to be a genetic mother is not unjust, nor does it preclude mothering. The question, then, is how much effort and expense we can justly dedicate to overcoming this dimension of infertility.

Paradoxically, OTC's discourse's queries about "the particular and the concrete" [1, p. 29] open more quickly onto these important questions than do the queries about gametes and abstract patient rights in which assisted reproduction discourse generally is so often mired. What OTC may teach us above all is a way of speaking that better comprehends the lives of real patients in the settings of their real, imperfect societies. Whether or not new births result from OTC, patients and society at large will benefit from this push toward constructive discourse.

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# Chapter 13
# The Lessons of Oncofertility for Assisted Reproduction

**Adrienne Asch**

## Introduction

Young children, adolescents, and men and women in their prime reproductive years may now survive for decades after cancer. They and their families celebrate these medical advances and hope that after cancer treatment ends, they can resume what Kathlyn Conway described as “ordinary life” [1]. When patients and their families learn that the treatments for some cancers can impair their fertility, they may feel that they will not be able to look forward to that ordinary life. No wonder, then, that many adult patients and parents of adolescents will rejoice at the medical and scientific developments that someday might permit them to have their own genetic children.

Like the symposium out of which it grew, this volume addresses the science and the ethics of dealing with cancer-related infertility. If the science and the medicine work, and 5, 10, or 20 years after surviving cancer some people are raising their own children, they may feel that they have had two miracles. They lived when once they might have died; and they have managed to create a new life and to extend themselves into a new generation. But as everyone in this volume acknowledges, there are no guarantees. Even the standard techniques using banked sperm and embryos do not always result in a baby, and using frozen oocytes and cryo-preserved ovarian tissue is still considered experimental.

Several contributors to this volume have explored a host of ethical and psychosocial issues that arise when people face both cancer and infertility. In what follows I extend their ideas and seek to make three main points: first, a great many of the concerns about handling cancer-related infertility apply to people whose infertility stems from other biological factors. Second, the medical response to cancer-related infertility should not remain the primary response, lest it perpetuate an unfortunate societal tendency to use technology to solve non-technological problems. Last, our

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support for medical cures for cancer, infertility, or anything else should not reinforce the conviction that there is only one kind of “ordinary” or “acceptable” life.

## How Is Cancer-Related Infertility Different from All Other Infertility?

Perhaps no disease or disability stirs people’s emotions as does cancer. AIDS and ALS are life-threatening, but in the developed world they are not as prevalent. Heart disease and stroke combined may cause more deaths than cancer, but heart disease and stroke usually occur in mid- or late-life. Everyone knows someone who has lived with or died from a form of cancer, and perhaps this prevalence in all ages, racial classifications, and socioeconomic strata means that people can readily empathize with patients and their families.

The general population may find it much harder to empathize with the reproductive problems of someone with little-known and stigmatized conditions such as spinal cord injury, cystic fibrosis, multiple sclerosis, or epilepsy [2]. Cancer, and cancer-related infertility, may seem to have come to a person for no reason, out of the blue, as contrasted with infertility that might be a consequence of personal behavior or inadequate health care.

Justifying the emphasis on medical research on oncofertility itself (Chapter 14 by McLoed, this volume), problems inherent in obtaining informed consent for fertility preservation (Chapter 19 by Cohn, this volume, Chapter 33 by Clayman and Galvin, this volume), permitting the retrieval and banking of oocytes prior to cancer treatment (Chapter 17 by Petropanagos, this volume), securing insurance coverage of infertility treatment (Chapter 29 by Campo-Engelstein, this volume), and removing barriers to adoptive parenthood (Chapter 11 by Gardino et al., this volume) illustrate the ethical questions found in this volume. Let me say why I believe that the link to cancer should not determine how we resolve most of them. Instead, their resolution flows from evaluating the essential components of the parent–child relationship.

Along with Carolyn McLeod (Chapter 14, this volume), I question the justification for putting extensive resources into oncofertility research. McLeod questions the empirical basis for the commitment to the research, suggesting that there are many problems with the studies used to support the claims that infertility is psychologically and socially devastating to women and men (especially to women); that biologic parenthood is a chief source of happiness; and that people who have had cancer, like people who have not had cancer, desire genetically related children. The force of her argument is not merely that there might be a weak empirical basis for the psychological harms of infertility. It is possible to listen to those “voices of the infertile” [3] who powerfully articulate their longing for genetic continuity between themselves and their children, and who dream of having a child who embodies their relationship with their partner, and yet maintain that such genetic connectedness is only one facet of any parent–child relationship. I want to go beyond questioning the empirical bases for justifying the oncofertility research to claim, as does McLeod, that the research gets its force from an unquestioned commitment to the moral and social centrality of the genetic basis of the family. Yet contributors to this volume who write about family and the difficulties of family decision-making for their minor children (Chapter 33 by Clayman and Galvin, this volume) note that less than half the children in the United States are living with the two people whose genes they carry.

After the genes have been passed along, what makes a parent–child relationship is the daily acts of physical, emotional, and financial support; the guidance and instruction in living in the culture and society; the time spent soothing, comforting, explaining, disciplining, and playing. People may indeed derive great pleasure from seeing their own or their relatives' physical characteristics in their children, but appreciating such resemblances is only a fraction of the ongoing involvement in bringing up a child. Consequently, the same considerations that justify concern about the medical research also warrant concern about whether any person could give genuinely informed consent to research or treatment. Cohn (Chapter 19 by Cohn, this volume) points out how difficult it is to convey uncertainties surrounding the treatment for cancer, to ascertain the possibilities that any specific fertility-preservation procedure will be effective in the individual case, and to evaluate the risks of delaying cancer treatment against the potential for future genetic parenthood. For a man or woman who already knows that he or she wants children within a few years, there may be very strong incentives to postpone cancer treatment to try to maximize the chances of achieving genetic connection to a future child; if the patient is in a relationship with a partner who expects to be the child's other parent, trying to create and store embryos before treatment may strike everyone as appropriate. But even in the medically easiest procedures of banking sperm or embryos that people expect to use in less than 10 years, how the doctors broach the topic of infertility can influence a patient's decision. If doctors equate infertility with the death of the dream of parenthood, they prevent the patient from imagining that they could contemplate forming a family through adoption or collaborative reproduction.

For the adolescents and young adults and their families who must absorb the news of cancer and then the news that the treatment may destroy genetic parenthood 20 or more years in the future, the difficulties of decision-making about saving fertility may be unique to cancer-related infertility. The treatment for the cancer, not the disease or disability itself, poses the fertility problem. The 14-year-old girl or the 17-year-old boy has been immersed in school, friends, and interests in sports, theater, or computers. Suddenly they learn they might die before college or their first job. If they live, they might not have children. Should they undergo more procedures to keep open the barely imaginable idea of child-raising? If their doctors and parents cannot help them understand that "family" and genetics are not identical, they may feel compelled to subject themselves to procedures they would rather avoid; they may believe they should gratify their parents' dreams of grandchildren when all they want to think about is avoiding any more pain and the anxiety of delaying treating the cancer itself. Alternatively, they may exert what little control they feel they have by opposing their parents and doctors who urge them to skip fertility-saving procedures based on a need for immediate cancer intervention.

Everyone who has spoken of the infertility preservation decision has underscored its time-sensitiveness. The urgency of decision-making so that cancer treatment goes forward quickly strikes me as the major difference between cancer-related infertility decision-making and decisions about treating infertility from other medical causes. There may be no way to give adolescents and their families more time between cancer diagnosis and the beginning of treatment. But doctors must work with parents and their young patients to help them recognize that they might become adoptive parents or step-parents, or that life can be full and rich without children. Doctors must help patients absorb their own and their parents' shock about the cancer itself, must underscore the uncertainties that they will benefit from effort at fertility preservation, and must confront the panic about lost reproductive capacity. As the only ones with the medical information about what awaits the young patient, they alone must defuse the drama surrounding the possible infertility and guard against overstating the "rescue" potential of novel therapies. Along with Cohn (Chapter 19 by Cohn, this volume) and Clayman and Galvin (Chapter 33 by Clayman and Galvin, this volume), I want to underscore the complexity of helping cancer patients and their families decide how much time, money, and emotion to invest in preserving possible genetic parenthood. But the difficulty of patient decision-making requires that the medical team spend more time in counseling patients, not only about the medicine but also about adoption and collaborative reproduction as legitimate means of forming parent–child relationships.

Contributors to this volume do not hold a unanimous view on whether there should be different policy responses to infertility following cancer treatment than to any other basis for infertility. Angel Petropanagos (Chapter 17 by Petropanagos, this volume) maintains that any woman, not just those facing cancer treatment, should be allowed to freeze her oocytes for future use. Petropanagos argues that the women whose infertility results from delaying childbearing for educational, financial, or career reasons have no more "choice" than the women who lose reproductive capacity from treating their cancer. Egg-freezing might lessen women's sense of having a "biological clock," and could give them some of the freedom men have always enjoyed about whether and when to reproduce. However, as I have discussed elsewhere [4], if many women freeze their eggs, this could divert attention away from the social structures that pressure women to delay child-bearing in the first place. Here is one instance where I think cancer-related infertility may merit sui generis policy.

A woman of 17, 25, or 33 years of age who discovers that she will lose her fertility in 2 or 3 weeks following cancer treatment has had no reason to bank her eggs. Although she may have delayed childbearing and parenthood for many reasons, before the diagnosis she expected that she still had several years of fertility left to her. There is more than a short "right" time for women to become genetic mothers if they so choose, but the woman infertile after cancer treatment has suddenly found that she has no more time to reproduce with her own genetic material. Treating an unexpected disease, not a maladaptive set of social institutions, has led to her infertility. By contrast, egg-freezing for age-related infertility uses biology to resolve a socially created problem. There is nothing inevitable or essential about the typical educational and work arrangements in the US, Canada, and other advanced societies. Societal endorsement of egg-freezing for women's biologically expectable, age-related infertility tacitly accepts unjust social arrangements and suggests that individual women should pay the physiologic and financial price for practices that favor men's lives.

Campo-Engelstein argues that treatment for cancer-related infertility is analogous to other treatments (wigs for hair loss and reconstructive surgery after mastectomy) that are commonly regarded as medically necessary. Although breast augmentation or diminution are usually considered elective cosmetic procedures and therefore not covered by health insurance plans, the surgery following cancer puts them in a different category, a response to an underlying illness. The same rationale warrants covering the costs of cancer-related fertility preservation through health insurance. The infertility is an inevitable part of some cancer treatment, beyond an individual's control. Campo-Engelstein makes a compelling case, but virtually all biologically based infertility is beyond an individual's control. As long as society does not condition receipt of health insurance coverage on alleged "responsibility" for illness, the costs of infertility treatment are arguably no less worthy of health insurance coverage than the costs of heart surgery that might have been prevented by diet and exercise.

Nonetheless, I would not endorse an automatic health insurance coverage of infertility treatment for cancer-related or any other biologically based infertility unless similar subsidies were available to people who chose to form families through adoption. Treatments for infertility do not usually restore the functioning of a body system; instead, they use the tools of science and medicine to create a child genetically related to at least one of the people who will raise that child. In keeping with my emphasis on the social, and not the genetic, component of the parent–child relationship, I would avoid coverage for only biologically based family creation.

Shauna Gardino (Chapter 11 by Gardino et al., this volume) looks at the barriers to adoptive parenting that have confronted cancer survivors. The vagaries of the adoption process, along with the scarcity of infants available for domestic adoption, lead many infertile people to risk medical procedures. Potentially intrusive home studies, adoption agency rules about parents' age, income, health, or disability status [2] can discourage those who might be happy to avoid fertility treatment and pursue adoption. The attention given to changing adoption practices that affect cancer survivors is laudable, but people with many other illnesses and disabilities deserve the same recognition as eligible potential parents. The cancer survivor and his wife may meet all the criteria of an adoption agency that is willing to look beyond the label of a medical diagnosis. But the same can be said for a woman with a spinal cord injury and her non-disabled husband [2]. They, too, deserve the careful scrutiny of any other would-be adoptive parents, but prejudices about how a parent's mobility, visual, psychiatric, or hearing impairment will adversely affect a child still thwart people with disabilities from attaining their parenting goals.

If the purpose of becoming a genetic or an adoptive parent is to have a deep, enduring, hopefully long-lasting relationship with a growing child, the matter of life expectancy after cancer cannot be ignored. Should someone with a life expectancy of less than 10 years undertake infertility treatment or adoptive parenting? This is a troubling question worthy of more sustained discussion by the oncofertility community. Parenting is more than procreation, the creation of genetically connected offspring. Rather than limit eligibility for adoption or infertility services based on predicted longevity, I would urge the oncofertility community to explore with would-be parents the provisions they will make for the care of their children if they cannot survive to see their child reach adulthood. A loving parent–child relationship, supported by other family and friends may provide the foundation for a child despite the loss of a father or mother before he is grown. But if parenting is, or should be, about forming a special relationship with a child, it seems reasonable to suggest that cancer patients with a life expectancy of less than a few years are not going to be able to help a child get started in life. Yes, children through the ages have lost parents during their infancy; mothers have died in childbirth, and fathers in war. That children survive such parental losses is not a justification for creating or adopting a child if one believes that his time is short.

Parenting gives an unparalleled opportunity to guide someone and foster her growth. Infertility treatments and adoption provide people who cannot reproduce without assistance to bring children into their lives. Parenting, however, is not the only way to make a difference to a young person. Teachers, relatives, and family friends often play crucial roles in children's lives, and many adults discover how fulfilled they can be in relating to children as less than a parent, far more than a casual acquaintance. The push for preserving fertility after cancer or other health problems should not obscure the richness of adult–child relationships beyond the parents.

For the same reasons that I urge health professionals to remind the infertile that genetic connection is not the only way to become a parent, I urge us all to remember that adults and children need a variety of connections. The infertile cancer survivor deserves social and professional support for finding non-parenting roles in children's lives. Rather than promoting options and choices for people after cancer, the emphasis on fertility preservation could inadvertently lead people to feel like failures if their efforts did not yield a genetically related child. The goal of oncofertility should not be enshrining one way to fulfill oneself, and should not lead anyone to conclude that there is only one "ordinary" or acceptable life.

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# Chapter 14
# Morally Justifying Oncofertility Research

**Carolyn McLeod**

## Introduction

Is research aimed at preserving the fertility of cancer patients morally justified? In response to this question, some people would resoundingly answer “yes.” Many oncofertility researchers and some survivors of cancer who are now infertile would probably react this way. But others might say “no,” in particular people who worry about the just distribution of scarce resources, the risks to patients and to their potential offspring of the relevant interventions [1], or pronatalist and other biases that seem to underlie this science. While I lean toward “no” myself, I recognize that the issue is complicated. I also believe that it must be confronted. Some people will try to dodge the issue by presuming that oncofertility research is justified, on the grounds that it promotes a basic right (to reproduce) or resembles research that our society has already condoned (i.e., research into other assisted reproductive technologies (ART)). But actually, there is no getting around the need to justify this research and to do so on moral as well as legal grounds. My concern specifically is with its *moral* justification.

In my view, a sound moral justification for oncofertility research is missing from the literature on oncofertility. Rather than fill this gap myself – which I think is impossible to do in a short space and which is also a job for an advocate, not a skeptic, of the science – my goal in what follows is to explain what I think such an argument must look like.

## Why Do the Research?

Moral justifications for oncofertility research often refer, understandably, to the suffering that cancer survivors experience if they are infertile because of their cancer treatments. Reproductive autonomy is relevant here, even though the focus is on

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suffering, not autonomy. The idea is that the potential for future suffering justifies giving cancer survivors the choice of whether to preserve their fertility and use the preserved gametes or tissue in the future to attempt to have their own genetically related children. I will give a representative example of such an argument, analyze it, and explain why it and arguments like it are flawed.[1]

The representative example comes from Philip Rosoff and Melanie Katsur [2]. The following is the positive argument they give for pursuing oncofertility research[2]:

P1) A common complication of cancer treatment is infertility.

P2) Infertility "can be [and often is] a devastating experience, especially for women" [3].

P3) Available data on cancer survivors and the clinical experience of one author suggest that cancer survivors are no different than the rest of us: many want genetically-related children[3] and infertility is or can be devastating for many of them, especially the women.

P4) Genetic parenting is "one of life's greatest fulfillments" [4].

C) Thus, providing cancer patients, especially female patients, with the chance of preserving their fertility is worthwhile, and this in itself justifies the research.

The overall concern here is with the happiness or life satisfaction of cancer survivors. The thought is that having genetic children will add significantly, and may in fact be essential, to their well-being. I take it that if asked whether oncofertility research is justified, many people would give a response similar to Rosoff's and Katsur's. But is their argument compelling? We should ask two things about it: first, are its premises all true? Second, does its conclusion follow logically from its premises? Beginning with the first question, I assume that we can accept P1, but what about P2–P4? What evidence do Rosoff and Katsur provide for their truth and is that evidence sufficient?

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[1] I do not look at reproductive rights arguments in favor of oncofertility research. I know of one such argument: that of Leilah Backhus and Laurie Zoloth in the last oncofertility volume [3]. According to Backhus and Zoloth, oncofertility research will protect people's right to reproduce, which they describe as an "important freedom within society that is seldom questioned or restricted" (166). They give a significant amount of weight to this freedom, which they justify by appealing to the work of John Robertson [4], but also by claiming that infertility is a disease or disability that people ought to have the freedom to overcome. I am doubtful that Backhus and Zoloth do enough to show that a right to reproduce justifies this research (especially if the right is negative, which is how a right to reproduce is normally understood, and if the science is publicly funded). But I do not engage with their argument here and thus do not show definitively that compelling arguments in favor of oncofertility science are absent from the literature.

[2] I have omitted their responses to reasons others might give for not doing this research; e.g., that patients could not meaningfully consent to it or that potential harms to offspring would be too great (16).

[3] Rosoff and Katsur use the expression "biological children" but I prefer instead "genetically-related" or "genetic children." In my view, the category of biologic children is larger than that of genetic children. Children to whom women give birth but to which they are not genetically related are still the women's biologic children because of a biological tie created during pregnancy. Fertility preservation can allow oncofertility patients to have genetic children, but may not be necessary for them (particularly for the female patients) to have biologic children.

The first of these premises, P2, has to do with how infertility impacts on people's lives. Many of us believe that infertility is or at least can be devastating, especially for women. Our grounds for this belief may be that people in general, but women in particular, have strong reproductive instincts that when thwarted cause them great suffering. Rosoff and Katsur make such a claim, and also bolster their argument with an appeal to psychological literature about the psychological distress that often accompanies infertility.

Let me comment first on the appeal to reproductive instinct. Insofar as we have such a drive, is it "rooted in biology" or in social conditioning [5]? Rosoff and Katsur's answer seems to be "both" [2]. But of course it is hard to know whether or how much biology plays a role here because society weighs in so heavily in favor of many of us having biologic children [6].[4] Social influences alone could explain why many people yearn for biologic children, why many view adoption as a last resort, and why many regard childlessness as a fate almost worse than death. Rosoff and Katsur suggest that the eventual frustration of a strong urge to procreate warrants a medical response: that of fertility preservation. Many people would oppose this move however if the procreative desire were entirely the product of socialization, although the move is questionable even with desires that are purely biological. One cannot justify a medical intervention simply by showing that it would prevent a strong desire from being frustrated, regardless of the origins of the desire and regardless of whether the person would be devastated if the desire were not satisfied. For example, risky and invasive cosmetic surgeries may not be justified even if women desire them intensely because they have been socialized to find their aging bodies disgusting. The same is true of extraordinary measures to keep dying children alive for which parents beg because of a powerful instinct to want their children alive. In short, claims about instinct may not show very much.

Nevertheless, that infertility prevents the satisfaction of a strong desire and thereby causes feelings of devastation could contribute to the justification of fertility preservation. But do we know that infertility has this effect? What proof do Rosoff and Katsur provide for such a claim? As I mentioned, they appeal to relevant work in psychology to try to substantiate P2. In particular, they refer favorably to an oft-cited paper by Arthur Greil, which critically reviews the literature on "infertility and psychological distress" [7]. However, among Greil's critical remarks about this literature is the observation that it focuses almost exclusively on those who seek treatment for their infertility. These people represent less than half of all infertile people in the United States, according to statistics gathered in 1995 [8]. Many of the psychological studies on which Greil comments focus even more narrowly on people who pursue IVF "and other 'high-tech' treatment options," that is, people who are predominantly "white, middle-class urbanites" [7] and who make up only 2% of all treatment seekers [8]. Consequently, the most we can conclude from the literature that Rosoff and Katsur cite is that infertility *can be* devastating (for women

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[4] Our society does not strongly encourage reproduction for everyone; it is anti-natalist toward certain groups, such as poor Black women [17].

in particular). Such a weak claim will not get us very far, however, in showing that oncofertility research is morally worthwhile. One would be hard pressed to justify the expense knowing that the research may only benefit a small number of people.

A further criticism Greil makes of studies about the psychological impact of infertility is that they have poor sample sizes. Unfortunately, this same criticism applies to studies about the desire of cancer survivors to reproduce. Rosoff and Katsur supply the latter studies as evidence in favor of P3, which concerns the extent to which cancer survivors want to procreate. For example, they cite a paper by Leslie Schover and colleagues that describes a survey of cancer survivor's attitudes on the subject [9]. These researchers conclude that 76% of the respondents who were "childless" wanted to reproduce (and by "childless" they surprisingly mean without biologic children[5]); but there were only 71 of these people, and only 132 respondents in total. Thus, while interesting perhaps, such studies cannot substantiate P3, for which Rosoff and Katsur do not provide sufficient evidence.[6]

The last premise to consider is P4, which says that genetic parenting is one of life's greatest fulfillments. People often make such a claim about parenting in general; yet for P4 to make sense in the context of Rosoff and Katsur's argument, it must be specific to genetic parenting. (Rosoff and Katsur do not state the claim very clearly and like Schover et al., sometimes forget that not all parenting is genetic or biological.) P4 is designed to show that cancer survivors have good reason to want to procreate or good reason to be devastated if they cannot procreate. In other words, P4 suggests that the desire mentioned in P3 (and also alluded to in P2) is worthwhile, objectively speaking.

Interestingly, Rosoff and Katsur provide no evidence for P4, which suggests that they believe its truth is self-evident. But is it obvious that biologic parenting contributes to a good life? The answer must be "no" if studies in psychology about well-being and parenting are to be taken seriously. These studies show consistent evidence of "an almost zero association between having children and happiness" or well-being [10]. In other words, they reveal that P4 could, quite simply, be false. Since I doubt many readers will accept that about P4, let me direct our attention to an absolute version of this premise: genetic parenting is *always* fulfilling. Such a statement is surely false. And so perhaps the claim should be that genetic parenting is fulfilling *other things being equal*: that is, only when certain conditions are present or others are absent. The question then becomes, however, what are the relevant conditions? Could one of them be the absence of a history of cancer? While this

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[5] Table 4 in their paper puts the total number "currently childless" at 71 (702), but their discussion reveals that ten of these people had stepchildren and two had adopted a child (701). To suggest that these 12 people are childless, and are therefore not parents, is false and potentially very offensive to them and their children.

[6] They also appeal to an article written by Schover alone, which reviews the "psychosocial aspects of infertility and decisions about reproduction in young cancer survivors" [18]. This article simply hypothesizes, however, rather than shows, that infertility is distressing for cancer survivors. Overall, in the oncofertility literature, there appears to be much speculation, and little hard data, about how cancer survivors feel about procreating [19].

may sound odd or insensitive, consider that after "battling pediatric cancer, many survivors endure numerous difficulties throughout their lives despite being cured of their disease. Fertility deficits are only one of the problems that they face..." [11]. Could it not be that parenting would simply add to the burdens of some (or many) cancer survivors?

My point is not that P4 is false, but rather that evidence needs to be marshaled in favor of it or of any other controversial premise in an argument that defends oncofertility research. Moreover, the evidence needs to be substantial, especially given how many resources are required for this research to happen. Proponents of the science cannot simply assume that most people have a strong procreative instinct, that cancer survivors are among these people, that procreation invariably contributes to a fulfilling life, and that therefore infertility is devastating for cancer survivors, even though they may be able to have children in other ways: that is, through adoption or the assistance of a gamete donor.

To be clear, the goal of oncofertility specialists is to preserve the capacity of cancer patients to become genetic parents, not to become parents of any kind. Granted, cancer survivors may confront barriers to becoming non-genetic parents. For example, they may face discrimination, de facto or otherwise, when attempting to adopt children [12]. But why not work to remove these barriers – more specifically to adoption – rather than to preserve the fertility of cancer patients? Perhaps we ought to do both, which is something that some members of the Oncofertility Consortium accept, despite their focus on fertility preservation. Why both, however, rather than just the one that allows for non-biologic parenthood (i.e., adoption)? To offset the bias that our society has toward biologic parenting [6, 13], perhaps we ought to encourage non-biologic parenting for infertile cancer survivors, for infertile people in general, or for everyone for that matter.

This discussion of different forms of parenthood is relevant in assessing whether Rosoff and Katsur's argument is valid. I have shown that they have not established the truth of their premises. Yet even if they had, one might ask whether we should accept their conclusion, (C), on the basis of the premises they give. Does the truth of their premises guarantee the truth of their conclusion? In other words, is their argument valid? I do not think that it is, for at least two reasons. First, assuming that resources are scarce, oncofertility research can only be justified if there are not other more worthwhile ways of allocating the resources that support it. But it is far from obvious that this is the case, especially given that the research may not be as worthwhile as Rosoff and Katsur suggest. Notice that the devastation some cancer survivors feel upon discovering that they are infertile could potentially be overcome through non-biologic parenting. There are psychological studies indicating that among infertile people who do fertility treatments that are unsuccessful, those who choose to adopt children have a greater degree of life satisfaction than those who do not [14, 15].[7] These adoptive parents (and I hope to be one of them

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[7] As with the studies about the desire of cancer survivors to procreate, the sample sizes with these studies are low. But notice that I use them to show only that a certain possibility exists, not that certain claims are true.

soon) could easily have levels of well-being similar to those of infertile people who succeed with fertility treatments.[8] Indeed, their experience may reveal that *adoptive* parenting is “one of life’s greatest fulfillments.” Rosoff and Katsur’s argument is not valid because it ignores this possibility and the implications it has for the just allocation of resources that are now being spent on oncofertility.

Second, Rosoff and Katsur want to say that the research should proceed with its mandate of preserving the fertility of cancer patients. However, what about women who want to reproduce but need to delay childbearing beyond the time at which they are most likely to be able to conceive a child without assistance? Rosoff and Katsur’s argument does not justify the scientists’ focus on the first group of women rather than the second (i.e., on fertility preservation for disease-related infertility rather than age-related infertility [16]). If we can construct versions of P1–P4 that apply to women who will likely suffer from age-related infertility, then presumably we cannot accept Rosoff and Katsur’s conclusion that oncofertility research ought to proceed. Consider the following:

P1) A common complication of being a career-aspiring woman is infertility.
P2) Infertility “can be [and often is] a devastating experience, especially for women.”
P3) Available data on career-aspiring women suggest that they are no different than the rest of us: many want genetically-related children and infertility is or can be devastating for many of them.
P4) Genetic parenting is “one of life’s greatest fulfillments.”
C) Thus, providing career-aspiring women with the possibility of preserving their fertility is worthwhile, and this in itself justifies research on fertility preservation.

Without a premise stating that we do not owe the same consideration to career-aspiring women that we do to female cancer patients, Rosoff and Katsur’s argument in favor of oncofertility research is invalid.

## Conclusion

To be sound, an argument in favor of oncofertility research must justify preserving the fertility of *cancer patients* specifically, despite the possibility of them becoming non-genetic parents, and despite the exorbitant cost of the research. Genetic parenthood *may be* essential to the well-being of many cancer survivors. Each survivor *may* even have a right to become a genetic parent (one that entitles him or her to have scientists develop oncofertility techniques using public funds). But neither of these claims is obvious, and each needs to be defended rigorously.

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[8] Some will say that these people would not have achieved such levels of well-being if they had not had the opportunity to resolve their infertility by undergoing infertility treatment. While it may, however, be true that (unsuccessful) treatment can help with resolving infertility, surely a resolution can come about in other ways. As far as I can tell, it is a myth that infertile people need to go through infertility treatment if only to resolve their infertility (see [8]).

Obviously, the sort of justification I believe is needed for oncofertility research does not presume that genetic parenthood is superior to other forms of parenthood. Such justification has rarely, if ever, been given for the development of other ART, such as in vitro fertilization. But this is no reason not to provide it for oncofertility research. Until that happens, the science will be on shaky moral ground.

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# Chapter 15
# Ethical Dilemmas in Oncofertility: An Exploration of Three Clinical Scenarios

**Clarisa R. Gracia, Jorge J.E. Gracia, and Shasha Chen**

## Introduction

As an emerging interdisciplinary field, oncofertility bridges oncology, reproductive endocrinology, and infertility with the goal of expanding reproductive options for women with cancer. Oncofertility is currently gaining significant attention from professionals in many related fields and is undergoing considerable scrutiny in part because of the many compelling ethical dilemmas it raises. To illustrate some of the dilemmas providers face, and make suggestions for clinical care, this chapter presents three clinical scenarios encountered in medical practice. An increased awareness of the complex problems involved should help prepare clinicians for some of the challenges posed by this rapidly expanding discipline.

While the three cases presented here are based on real-life situations, they have been modified to protect the identity of the patients involved. The cases raise the diverse, and sometimes overlapping, problems that surface in the clinical environment, highlighting different ethical dilemmas faced by physicians. For the sake of brevity, we have chosen to explore only two problems in each of the first two cases and one in the third. Each dilemma is presented in the form of a question to capture a central point, although in fact the cases are complicated and involve many variables. Two alternative courses of action in each case appear unavoidable but also unacceptable, creating a seemingly unresolvable situation for the clinician. The question is what can physicians do under these circumstances to satisfy the requirements of their ethical responsibility? Can they escape the pitfalls of the dilemmas and find ethically satisfactory courses of action?

After presenting each of the three cases, we discuss them and highlight the dilemmas they pose. We then present three theoretical strategies commonly used in ethics. Two of these, deontology and consequentialism, fail to resolve the dilemmas, but a

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third, namely virtue ethics, appears promising. Finally, we suggest some practical steps that should help physicians move closer to a resolution of their quandaries.

## Case 1: Description

Alice is a 15-year-old Chinese American female with a history of Hodgkin's lymphoma who was found to have recurrent lymphoma several months after chemotherapy. A bone marrow transplant had been advised by her oncologist, a treatment that would almost certainly result in permanent infertility. While her oncologist had discussed this risk with her parents, neither the physician nor her parents had discussed the risk with Alice or had given her the option of pursuing methods to preserve her fertility. However, a day before her scheduled bone marrow transplant, she learned through the internet that the procedure would likely render her sterile. She then confronted her parents and physicians and asked if she could pursue fertility preservation options. Ultimately, she was referred for a fertility preservation consultation and banked ovarian tissue. Unfortunately, because of the late decision to proceed with fertility preservation and limited availability at the transplant center, her bone marrow transplant was significantly delayed, with the potential to worsen her long-term prognosis.

## *Who Should Make Decisions in Adolescent Medical Care: Adolescent Patients or Parents?*

It is generally believed that a therapeutic patient–physician relationship consists of a partnership in which both parties participate actively to make medical decisions. "Patients have a right to know about their health, to know about available diagnostic and treatment options and their risks and probable benefits, and to choose among the alternatives" [1]. While these principles apply to competent individuals at least 18 years of age, the role of the adolescent patient in medical decisions remains ambiguous primarily because the United States legal system generally does not give adolescents autonomy unless they are considered emancipated minors, mature minors, or are seeking treatment for specific disorders [2]. Patient autonomy is commonly understood to mean that a patient has the capacity to act intentionally, with understanding, and without controlling influences that undermine a free and voluntary act. This principle is at the basis of "informed consent" in the physician–patient transactions regarding health care.

Because there is evidence that most minors age 15 and older are able to understand concepts about treatment alternatives and provide informed consent, the American Academy of Pediatrics has recommended that physicians involve adolescents in the medical decision making process [1–3]. Adolescents are generally asked to provide "assent," an indication that they are participants in the process, although they do not have absolute autonomy in decision making. However, it is not always the case that adolescent patients are fully informed of all of the risks, benefits, and alternatives of treatment so that satisfactory decisions can be made.

The reality of clinical practice is that adolescents are often not informed of the reproductive consequences of cancer therapy and potential options to mitigate these long-term effects [4, 5] because physicians feel they need to defer to the authority of parents/guardians. In our case, while Alice's parents were fully informed of all of the reproductive risks of the recommended cancer treatment, the patient was not. Reasons for nondisclosure may include a primary focus on curing the cancer rather than on long-term quality of life, a desire to protect the child from anxiety, discomfort in discussing sensitive issues such as future sexuality and childbearing, and the limitations of fertility preservation methods. One study reports that about half of the physicians interviewed said that the cancer diagnosis causes such shock that issues like fertility are often put on the "back burner" [4]. Infertility is generally not emphasized as a major risk of cancer therapy and therefore does not get the same attention as other health risks such as cardiac damage, cognitive impairment, or new malignancies; it simply is not something patients and family members think of when cancer is diagnosed [6]. A survey of teens and young adult women undergoing cancer treatment reports that a minority of these young patients are satisfied with the information they received about cancer-related infertility from their oncology team and a third to half of the teens cannot recall any discussion of such topic [7].

Failure to disclose such information to adolescents prevents them from participating in decision making. In Case 1, nondisclosure led to a significant delay in life-saving cancer treatment because the patient wanted to pursue fertility preservation. On the one hand, given that fertility preservation technology is becoming more widely available and publicized [8], failure to discuss these options might lead to substantial future anger and resentment toward parents and physicians. On the other hand, overemphasis on reproductive consequences and lack of appropriate follow-up leads some adolescents to assume that their treatments have left them infertile. This in turn prompts them to stop using contraception, which can result in unplanned pregnancies [7].

## *Should a Physician Abide by or Reject Different Cultural Traditions with Respect to Disclosure and Medical Decision Making?*

The cultural perspectives of patients and families can also influence the patient–physician relationship. The Chinese cultural background of the family depicted in the clinical scenario in this case may have played a major role in the communication barriers that occurred between the individuals involved. Although in East Asian cultures, especially those of Japan and China/Taiwan, the concept of telling the truth is highly valued, the situation is different in the context of serious medical conditions [9–11]. In these Asian countries, a "family consent for disclosure" is commonly adopted as a way of transmitting information in a health context, where a physician must respect the family's wishes and often act on the family's accord in the treatment of a patient [10]. Consistent with Chinese culture, many believe that in serious illnesses, revealing the diagnosis to patients results only in hopelessness and may actually hinder recovery [12, 13]. Among members of these cultures or ethnic groups, families do not consider nondisclosure to the patient to be morally objectionable, but rather perceive it as a form of protection [9]. Physicians often reveal the complete diagnosis only to the families, whose members have the primary responsibility to disclose to patients what they deem appropriate. Although this is quite contrary to modern mainstream medical practice in the United States, where full disclosure and informed patient consent by physicians to patients is the norm, much of the rest of the world continues the cultural practice of nondisclosure in medically serious conditions.

In Case 1, the parents may have concealed aspects of their child's diagnosis and treatment because they believed that informing her of all the risks of her illness and treatment would be detrimental to her recovery. They acted on what they considered to be the best interest of their daughter, rather than telling her the truth about her condition and the risks for future childbearing. This lapse in the proper transmission of information from the Western point of view between the parents and the child would not have been problematic had the child shared the values of her parents. However, this was not the case, for the patient became extremely concerned with her treatment upon learning of its risks for future childbearing. Such differences in opinion between parents and adolescent children may be due to generational and/or cultural gaps that exist [14]. Whereas the parents still identified principally with Chinese culture, the Chinese-American daughter had been raised in a vastly different environment, with different social values. The ethical dilemma for physicians facing such clinical situations lies in whether they should respect the cultural norms of parents and allow them to decide what information to disclose to their teenage children or to enforce full disclosure. Undoubtedly it can be challenging for physicians to refuse the wishes of parents who feel that they have their children's best interest in mind, sincerely believe that their approach is the best, and have cultural traditions dating back hundreds of years.

## Case 2: Description

Lisa is a 32-year-old recently married woman diagnosed with metastatic breast cancer. Prior to her cancer treatment, she pursued IVF and banked nine embryos. Unfortunately, despite aggressive cancer therapy, she died a year later. The embryos were left at her husband's discretion and initially he was unable to make a decision about disposition. He did not wish to have the embryos placed in a gestational carrier, donate them to another couple, discard them, or continue paying for storage. He has not paid for storage for 6 months and now the clinic cannot reach him.

## *Should Cancer Patients with Poor Prognosis Be Allowed to Pursue Fertility Preservation or Should They Be Denied Treatment?*

Most females of reproductive age with cancer have an excellent chance of survival and many will eventually be healthy enough to use cryopreserved gametes and embryos [8, 15, 16]. Moreover, since having biological children is highly valued and important for long-term quality of life for many individuals, fertility preservation can be justified in most cancer patients of reproductive age. However, there are situations, such as the one in Case 2, in which patients have a very poor prognosis and may never have the opportunity to use the gametes or embryos. One might argue, based on considerations of fairness, that it is an unwise utilization of resources to allow cancer patients with low likelihood of survival to pursue methods of fertility preservation insofar as it is very likely that the embryos would remain unused and those resources could be better used by others. Another argument against fertility preservation in a case such as this is that the procedure may instill an unrealistic sense of hope in patients, and this might be detrimental because it may prevent patients from accepting the severity of their illness. A contrasting view is that providing patients with a sense of control and hope may actually be therapeutic and help them cope with the illness. Fertility preservation might also be important for partners and family who wish to keep the memory of a loved one alive through a future child. Finally, denying care based on prognosis can be difficult because it requires clinicians to draw a line on eligibility. What should be the estimated prognosis of a patient in order to offer fertility preservation, and who will determine the prognosis especially when there is limited data available?

## *Should Physicians Discard Abandoned Frozen Embryos and Gametes or Continue Their Cryopreservation?*

The questions surrounding the treatment and storage of frozen embryos are not unique to oncofertility, as excess embryos are stored routinely as part of in vitro fertilization (IVF) for the treatment of infertility. A 2007 survey conducted by the American Society for Assisted Reproductive Technology estimated that over 400,000 frozen embryos were being held in cryopreservation storage facilities in the United States [17]. As fertility preservation becomes more available, there will be an increasing number of embryos and gametes in long-term storage facilities and IVF clinics. In oncofertility, it is anticipated that not all gametes and embryos will be utilized to achieve a pregnancy since cancer patients may die, conceive on their own, or decide not to pursue childbearing. Moreover, the long lag time between cryopreservation and clinical use increases the potential for loss of contact and therefore makes embryo and gamete abandonment likely as well. The potential for unclaimed frozen embryos and gametes in storage facilities raises ethical problems. Couples generally state their wishes regarding embryo disposition in writing prior to storage. They are given three options in case of death of each parent: donation to research, donation to another couple, or destruction. However, often little attention is given to this process, especially when patients are overwhelmed with a recent cancer diagnosis and are rushing to pursue fertility preservation methods prior to cancer treatment. The focus is on curing the patient and preserving future fertility, rather than planning on case of death. Case 2 illustrates how difficult it can be to decide on disposition of embryos after the death of a spouse. In this case, rather than make a decision, the husband abandoned the embryos.

In situations in which the partners are uncomfortable with the three options mentioned and prefer to keep the embryos in storage, even though they are not willing to pay for the cost, is it ethical to discard the embryos? The position of the Ethics Committee of the ASRM is that it is reasonable to destroy embryos “if more than 5 years have passed since contact with the couple, diligent efforts have been to contact the couple… and no written instruction from the couple exists concerning disposition” [18]. Still, although it might be reasonable and legally defensible to discard such embryos and gametes, many IVF clinics feel uncomfortable with this practice and continue to store abandoned embryos indefinitely insofar as they feel the embryos have intrinsic value [19]. While the disposal of abandoned gametes and ovarian tissue may be considered less problematic because these are generally not given moral status, there is no question that these tissues also have value insofar as they represent the potential for a future biologic child.

## Case 3: Description

Michelle is a 28-year-old patient with severe mixed connective tissue disease and multiple medical problems including pulmonary hypertension. Due to the severity of her illness, she had been advised to pursue an experimental regimen normally used to treat cancer that included high dose gonadotoxic chemotherapy as well as a bone marrow transplant. Michelle is a highly educated individual and had done extensive research regarding this treatment and understood the almost certain risk of future infertility and premature ovarian failure. Therefore, she was intent on banking eggs prior to treatment even though she realized that she might never be healthy enough to carry a pregnancy and would need to use a gestational carrier. After being medically cleared by her physicians, she underwent ovarian stimulation and 12 mature eggs were successfully frozen. However, 2 days following the fertility preservation (FP) procedure, she was admitted to the hospital with high fever and respiratory distress and had a complicated hospital stay due to the severity of her mixed connective tissue disease. Her recovery was very slow and ultimately she had to delay the treatment of her underlying disease.

### *Should Patients with Medically Complicated Conditions Be Offered or Denied Methods to Preserve Fertility?*

As fertility preservation methods become more widely available, demand is increasing even among patients without cancer who suffer from other conditions that might affect future fertility. This phenomenon has broadened the application of fertility preservation techniques to many medically complicated patients who would not normally pursue these procedures and, like the patient in Case 1, place a very high value on the potential to have a biologic child in the future. Unlike most young women with cancer or infertility for whom these procedures pose very little risk, these procedures can involve significant health hazards in medically complicated patients. Indeed, as in the scenario described in Case 3, proceeding with ovarian stimulation and egg banking can result in many serious complications, even death. The risks and benefits of fertility preservation procedures can be difficult to balance, particularly in cases such as Michelle's, because it is not clear what the actual risk might be to the patients' health. In Michelle's case, had the physician known that she would become critically ill after the procedure, thus delaying potentially life-saving treatment, then it would have been ethically justifiable to deny her fertility preservation options. However, her poor outcome was not foreseeable. And, although alternatives such as adoption may appear to be an excellent long-term solution for having a family in the future for such patients, it must be recognized that the illness itself might prohibit the women from adopting children so that this option may not actually be a viable alternative (See Chapter 34 by Gardino and Emanuel in this book). So how should physicians better counsel patients and establish rules of consent for fertility procedures in patients who have complicated medical conditions and for whom there is no safety data? Can a clear line of eligibility be drawn? And when should patients be excluded from fertility preservation options due to their health?

## Theoretical Strategies

Ethicists have developed a number of strategies in response to these matters, none of which is universally accepted or above criticism. From the many available, we have chosen three to illustrate how they attempt to escape the dilemmas considered here. Two of these are quite popular, but in the end do not appear to work well in the cases we have discussed. They go by the names of *deontology* and *consequentialism*. The third, known as *virtue ethics,* has more promise [20].

According to the deontological strategy, in order for actions to be ethically sound, they must be made on the basis of principles that are worthy in themselves, apart from any consideration of the consequences that those actions may have. In Case 3, for example, the autonomy of the patient is a good in itself and as such must be respected by the physician, even if the patient uses her autonomy to reach decisions that will cause her harm. Prima facie, this approach appears to dissolve the quandary of the physician. In spite of the patient's condition and any possible outcomes, the physician must honor the patient's autonomy, and thus implement her wishes. In doing so the physician acts ethically.

Although this course of action sounds both idealistic, insofar as the physician acts according to principle, and convenient, insofar as the physician's role and responsibility are clearly defined, the situation is not as simple as it appears. Two problems make this clear. The first is that there are more than one principle at play in this situation. Certainly the Principle of Autonomy is a worthy one, but there is also the Principle of Nonmaleficence, which states that a physician should not cause harm to a patient. And if the physician knows that the procedure the patient wishes to have is likely to cause her harm, then the physician must choose between the two principles, thus still facing an ethical dilemma.

The second problem is that it makes no intuitive sense to argue that the ethical value of an action relies fundamentally on a matter of principle and has nothing or little to do with its consequences. Indeed, is it not a matter of common sense that we judge many actions to be morally reprehensible precisely because they cause harm? Can we really hold that an action that causes no harm at all is as morally bad as one that causes harm? It seems to make little sense to talk about the worth of principles apart from consequences in a medical context in which the whole enterprise is predicated on weighing what is better or worse for patients.

It is problems such as these that lead other ethicists to reject deontology and defend consequentialism instead. This strategy argues that the ethical value of actions should be measured exclusively by their consequences. If fertility treatment in a cancer patient has better results than no treatment, then the decision to treat the patient is ethically sound. But if its consequences are worse than no treatment, then the decision to proceed with the treatment is ethically unsound. The value of this approach is that it brings back into the picture the benefit of the patient. For Case 1, if respecting the culture of the parents, and not informing the patient of the consequences of her treatment, results in harm to the patient, namely, permanent future infertility, then the decision is ethically unsound. Physicians, so the argument goes, need to focus on the results of the procedures they recommend, rather than on the ideal worth of any abstract principles they may use.

However, this strategy also runs into difficulty on many counts, two of which are quite evident. The first is that the consequences of the actions taken by physicians regarding treatment of their patients are often not known to the physicians prior to the treatment. This is evident in Case 3, where the condition the patient developed after infertility treatment was only a possibility among many, and became a reality only after the treatment was implemented. How can a physician determine and choose the ethically sound decision before he or she knows what will actually happen to the patient? Patients are unique in many ways and their health is affected by many variables, some of which are not measurable and unknown at the time a decision concerning a treatment must be made. For this reason, it makes no sense to base ethical responsibility on factors that lie outside the information accessible to a physician.

The second problem with consequentialism is that it is quite impossible to measure all the consequences of any action. The actions physicians take have innumerable consequences. Some of these affect the patients, but others affect other people, such as partners, members of families, and even society at large. This is quite evident when we consider such things as the cost of egg preservation over the long run, as we saw in Case 2. And who can measure all these consequences? How can a physician be expected to act ethically, if the ethical value of the action is contingent on such an innumerable, and mostly unavailable, number of consequences of the actions?

In short, consequentialism does not help physicians resolve the dilemmas posed by the three cases we have examined. Indeed, neither consequentialism nor deontology offers effective guidance in resolving them, and in some ways, they make matters worse.

This leaves us with the strategy we think has the most promise, the virtue ethics option. According to this point of view, the key element in the resolution of ethical dilemmas such as the ones physicians face in the three cases presented here, is the physicians themselves. Principles and consequences are important only to the extent that they play a role in the deliberations in which physicians engage prior to their decisions. Ultimately, physicians determine the best course of action. This makes physicians, their training, and their character, essential in medical ethics and underscores the need for their proper training and education, not only in physical diseases, but also in mental health, social issues, and ethics. The authority of physicians is based on their accumulated knowledge and experience. A virtue ethics approach does not entail a free ride for physicians, or a view that whatever they do is right. In fact, this approach puts a heavy burden on them to accept and exercise their responsibilities with utmost care, based on sound practice.

This position is called virtue ethics because it bases ethical behavior on what a person with the proper training and education would do, which in this context refers to the physician. Of course, not all physicians are equally well trained or educated, or have the proper experience, a reason why consultation among physicians is essential, as is the supervision of younger physicians by older ones. There is no substitute for experience. If you want your kitchen faucet fixed, it is better to have someone who has fixed 1,000 kitchen faucets do it than to have someone who can describe how to do it well, but has never fixed one. Likewise, it is the physician in the field, the one who has experience of many cases, who is most competent to decide the course of action in any particular case. What makes these decisions particularly challenging in a new field like oncofertility is that physicians with long-term experience are scarce.

The virtue ethics approach has a number of advantages over the two others we have considered. One advantage is that it incorporates the other two theories insofar as properly trained physicians will consider consequences, as far as they can be known, as well as principles. Another is that it gives physicians the authority to act, with full knowledge that sometimes outcomes may not be ideal. And a third is that it individualizes decisions, focusing on the particularities of the cases. An experienced physician with the proper training should be able to broker a deal between the ethnic parents and the adolescent of Case 1, determine what is best in terms of treatment for the seriously ill patient of Case 2 and her preserved eggs, and judge the right course of action when it comes to the treatment of the patient with the medically complex condition of Case 3. To repeat, this approach does not absolve physicians from responsibility, but rather it recognizes their authority and gives them the freedom to act according to their best judgment and without regret.

## Practical Strategies

Apart from the theoretical strategies discussed above, there are some practical steps that help physicians deal with the dilemmas they face in the practice of oncofertility. Moreover, they fit well with the virtue ethics approach we have suggested insofar as they require a case-by-case and individual approach, based on experience and training. We offer first some general guidelines that apply throughout the practice of the discipline and then we turn to specific recommendations that apply to the cases presented here.

First, physicians must be keenly aware of the particular kinds of problems reflected in these clinical scenarios, for it is ultimately the responsibility of physicians to recognize and address these problems before any treatment is initiated. Second, a team approach to counseling is most helpful, in which reproductive endocrinologists, oncologists, nurses, and mental health professionals discuss fertility preservation options over several visits if time permits. This allows for a more comprehensive evaluation to explore and understand family dynamics, values, and cultural issues. And third, understanding a patient's perspective is critical in establishing a therapeutic patient–physician relationship in which both parties not only discuss the risks, benefits, and alternatives of fertility preservation, but long-term prognosis, and disposition of tissues.

## Specific Suggestions for Case 1

### *Who Should Make Decisions About Adolescent Medical Care and to What Extent Should Cultural Factors Play a Role in Informing Patients of Their Condition?*

This case highlights how the ethical dilemmas faced by physicians taking care of adolescents with cancer are largely the result of communication barriers between physicians, the patients' parents/guardians, and the patients themselves. Removing such barriers through enhanced physician awareness and comprehensive communication is an effective way for physicians to tackle the dilemmas in this situation [5].

In adolescent cases, physicians should work to establish close relationships with both patients and their parents/guardians so that true, shared decision making can take place [14, 21, 22]. It is important to include adolescents in the conversation and listen to their perspectives. Such an approach should allow all parties to discuss the options openly and come up with solutions that are acceptable to everyone. Since every situation is unique, counseling should be individualized. The cultural/ethnic background of the patients and potential disparities between the point of views of families and patients must be taken into account, but ultimately should not interfere with establishing a therapeutic relationship between the physician and patient. If differences in opinion occur between parents and minors, then physicians should serve as mediators and try to balance the autonomy of the minors, the best interests of the minors, the parents' values, and the law. Legal intervention should be a last resort [2].

## Specific Suggestions for Case 2

### *Should Cancer Patients with Poor Prognosis Be Allowed to Pursue Fertility Preservation?*

Physicians should to take into account the long-term prognosis of patients when counseling about fertility preservation. An open and honest discussion of the potential for survival and pregnancy not only helps in the decision making process, but also prepares patients for their treatment and helps them to consider the future realistically. It is our experience that many such patients will decide against fertility preservation after a thorough discussion has taken place. Nonetheless, we do not believe that strict criteria should be applied to prognosis since this is often not practical. Consultation and collaboration with the oncologist will help guide these discussions. Even if the prognosis is poor, a patient's wishes should not be altogether ignored. Counseling should be provided throughout, and fertility preservation may be considered as long as the patient has a full understanding of her situation and the potential risks involved [21].

### *What Should Be Done with Abandoned Frozen Embryos and Gametes?*

To prevent uncertainty about gamete and embryo disposition, it is critical that physicians fully address this issue before performing any fertility preservation procedures. A clear understanding and documentation of the wishes of cancer patients and their partners must take place. This should include instructions concerning the "disposition in case of death, divorce, separation, failure to pay storage charges, inability to agree on disposition in the future, or lack of contact with the program" [18]. Clear instructions on disposition in case of abandonment can help to prevent the ethical dilemma of embryo and gamete disposition. Because cancer patients may store tissues for long periods, even decades, it is important that IVF clinics maintain regular contact with patients. These steps do not always absolve physicians from the dilemmas posed by Case 2, but they do ameliorate the situation and help physicians fulfill their ethical responsibilities. Consultations with a mental health professional concerning patient and partner preferences for disposition should also be encouraged.

## Specific Suggestions for Case 3

### *Should Patients with Medically Complicated Conditions Be Offered Methods to Preserve Fertility?*

Physicians must strike a delicate balance between the patient's autonomy and minimizing risks to the patient. As with the previous cases, establishing a strong relationship between the patient and physician will allow for an open discussion of potential risks, benefits, and alternatives to treatment. Since a reproductive endocrinologist does not have the requisite experience to manage patients with complex medical problems, it is important to seek recommendations from physicians caring for the patient and perhaps ask for additional pertinent opinions. In the clinical scenario presented in this case, understanding the patient's motivation for pursuing the procedure is also important because she was informed of the low probability that she would ever be able to carry the pregnancy and most likely would have to use a gestational carrier but still insisted on the fertility preservation treatment. The physician must make sure that the patient's resolve in cases such as this is not an indication that she does not fully grasp the severity of her situation. Psychosocial counseling is invaluable in such cases in order to ensure that the patient has decisional capacity and is making a reasonably informed choice. In cases where a physician feels that the risk outweighs the benefit, it may be necessary to deny care or refer the patient to another provider. When physicians are undecided about how to proceed, it may be helpful to seek advice from an ethics committee.

## Conclusion

The theoretical approach and practical steps suggested in the three cases we have discussed should help physicians deal with some of the ethical difficulties they face in making decisions about patients in the field of oncofertility. In particular, the emphasis on communication, counseling, development of awareness of cultural background, considering patient prognosis, and collaboration with other allied health providers should help resolve some situations and lead physicians to reach reasonable decisions and make good recommendations. However, these steps do not completely eliminate the dilemmas physicians face. As demonstrated in the three cases we have presented, physicians have to make decisions to the best of their ability, even though these choices may not be acceptable to all parties involved or completely beneficial for all. In short, the ethical dilemmas do not disappear completely and it is the duty of the physician to weigh the risks, benefits, and wishes of patients and families to guide them to the best course of action. Ultimately, a better understanding of the complex ethical, social, and medical issues in oncofertility is needed. As this field grows, continued multi-disciplinary research and clinical experience will help to inform good clinical practice.

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# Chapter 16
# Participation in Investigational Fertility Preservation Research: A Feminist Research Ethics Approach

**Michelle L. McGowan**

## Introduction

The goals and rhetoric of The Oncofertility Consortium [1] are aimed toward preserving cancer patients' reproductive choices and facilitating their reproductive autonomy after cancer. While the end goals of oncofertility research are oriented toward safeguarding the possibility of biological reproduction for women and girls facing cancer treatments that may affect their reproductive capacity, considerable basic and clinical research is still needed in order for oocyte cryopreservation, in vitro follicle maturation, and ovarian tissue cryopreservation to become established fertility preservation techniques. In fact, at the time of writing, all of the professional organizations that have published guidelines on fertility preservation techniques consider embryo cryopreservation to be the only established fertility preservation method utilizing assisted reproductive technology (ART), while oocyte and ovarian tissue cryopreservation are considered investigational or experimental techniques that should only be offered under Institutional Review Board (IRB)-approved research protocols [2–8].

The Ethics Committee of the American Society for Reproductive Medicine (ASRM) argues that additional research is needed to assess the safety and efficacy of these investigational methods in IRB-approved human trials with cancer patients [4]. Further clinical research with these patients will help to determine the optimal patient population, techniques for collecting tissue, and protocols for cryopreservation and in vitro follicle maturation [8]. In addition, human oocytes and ovarian tissue are needed in order to conduct basic research to establish the appropriate patient population, methods of tissue collection, and cryopreservation and maturation techniques that will help the oncofertility enterprise move these techniques from investigational to established methods of fertility preservation [3, 8].

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From a feminist research ethics perspective, the ethical standards for conducting both basic and clinical research must include but also go beyond ensuring IRB approval of human subjects research and collating evidence of safety and efficacy. To proceed with fertility preservation research in an ethical and just manner, it is also important to ask the following: (1) on whose bodies is fertility preservation research dependant? and (2) in selecting research subject populations, how should researchers balance the risks and benefits to prospective participants? This chapter applies a feminist research ethics approach to the oncofertility context, with a particular focus on the sources of oocytes and ovarian tissue for investigational fertility preservation research and the potential vulnerabilities of participating in this research.

## Feminist Approaches to ART and Biomedical Research

As women's bodies are the site of the bulk of reproductive interventions, feminists have had a long-standing interest in ART that has evolved around the differential physical burdens that women and men experience in fertility treatments [9]. In her review of feminist literature on infertility, Charis Thompson has argued that most of the early feminist writings on ART expressed "moral certainty" that hi-tech reproduction was bad for women, but since roughly the early 1990s there has been a shift in the feminist literature toward "moral ambivalence" regarding these technologies [9]. Thompson marked a gradual shift in the feminist literature "from easy condemnations toward multiplicities of women's experiences of reproductive technologies" [9, p. 69] as responsiveness to growing claims by women using ART that these technologies enabled them to exercise reproductive choice and feminist acknowledgement that individuals have varied encounters with reproductive medicine depending on their positionality in society [10]. Despite this shift in tone, the feminist work on reproductive technologies has continued to caution that the dominant cultural narrative that normative womanhood includes and even mandates motherhood has maintained the "need" for ART, and helped it to grow, especially for some sectors of the population [9, 16–19].

An outgrowth of feminist analysis of ART has been the feminist scholarship on biomedical research that involves reproductive material. To date, these feminist analyses have primary focused on the use of embryos and oocytes for human embryonic stem cell (hESC) and somatic cell nuclear transfer (SCNT) research. Existing feminist critiques of hESC and SCNT research have been leveled at the potential risks to and commodification of women's bodies in the reproductive labor required to produce oocytes for research [9, 16, 17] and the potential for coercion of women and their partners who have spare embryos from in vitro fertilization (IVF) treatments that could be donated for research [20, 21]. Catherine Waldby has also raised concerns that the growing demand for oocytes for SCNT research has the potential to exploit already impoverished women as sources of oocytes since ART is differentially regulated globally and regulations regarding financial compensation for oocytes vary from country to country [19]. Because both IVF patients and healthy research volunteers are possible providers of oocytes for research purposes, Angela Ballantyne and Sheryl de Lacey have argued that it is important to consider the different circumstances under which each of these populations of women may come to provide oocytes for research, and that each source of oocytes requires its own research ethics guidelines to ensure just selection of participants in research involving reproductive materials [22].

## Oncofertility: Patients, Basic Research, and Clinical Research

Oncofertility research sits at a crossroads between basic biomedical research and clinical research on emerging forms of ART, which makes it a particularly interesting site for feminist analysis of research involving reproductive materials. In some ways, oncofertility research is similar to hESC and SCNT research because reproductive materials are needed for basic research on fertility preservation techniques. In other ways, oncofertility research is more like ART research because both involve clinical research with patients who could directly benefit from the fertility techniques being "investigated" on their bodies. However, while the basic research involved in hESC and SCNT is meant to generate generalizable medical knowledge for the development of stem cell therapies for a range of medical conditions [22] and ART procedures have primarily been integrated into commercial clinical practice without prior establishment of safety and efficacy in primate models [23, 24], oncofertility research has been designed to evolve through collaboration between basic research and a systematic multi-site clinical-trial model which can yield guidelines for fertility preservation protocols specifically for cancer patients [24]. In light of these unique characteristics of oncofertility research, Laurie Zoloth has described a triple role for women and girls with cancer participating in investigational oncofertility protocols as patients, human subjects in clinical research, and tissue providers for basic research (Zoloth, this volume) This raises the question: given their triple roles as patients, tissue donors for basic research and as human subjects in clinical research, are cancer patients the most appropriate population to be participating in research on investigational fertility preservation techniques? What particular risks and vulnerabilities does this population face in these roles, and how might they be mitigated? And if this is not the most appropriate research subject population, who might be? The following section will explore these questions in depth.

## Potential Participants in Investigational Fertility Preservation Research

Writing about the ethics of oocyte provision for stem cell research, Ballantyne and de Lacey have argued that a feminist research ethics framework requires careful attention to selection of research participants. They explain:

> The principle of 'just participant selection' requires that research subjects be selected from the population that stands to benefit from the research. Based on this principle, infertile women should be actively recruited to donate eggs for fertility-related research *only*. It is unethical to exclusively or predominantly recruit infertile women to donate eggs for stem cell research that concerns general medical conditions. It is preferable to recruit women from the general population to donate eggs for such research, and these women should be viewed as healthy volunteers. To avoid exploitation, these donors should receive compensation for both the direct and indirect costs associated with their donation [22, p. 145].

For the purpose of my analysis, I will consider the applicability of Ballantyne and de Lacey's framework of just research participant selection to the context of investigational fertility preservation research, with a particular focus on oocyte cryopreservation and ovarian tissue cryopreservation. Populations who have participated or who have been proposed as potential participants in investigational fertility preservation research thus far include cancer patients, fertility patients, women who are already donating oocytes for reproduction, and healthy research volunteers providing oocytes or ovarian tissue specifically for research. Each population will be considered in turn.

## *Cancer Patients*

Patients seeking fertility preservation in light of a cancer diagnosis may be faced with a decision regarding whether to participate in an investigational fertility preservation protocol. Currently both basic and clinical research involving ovarian tissue cryopreservation rely almost exclusively on cancer patients as research participants and sources of ovarian tissue [25]. Practice guidelines allow for up to 20% of ovarian tissue collected for fertility preservation to be allocated for basic research to improve the technique, and the rest of the ovarian tissue is cryopreserved for the patient's future reproductive use in the event that her cancer treatments result in ovarian failure [26, 27].

To apply the framework of just participant selection to fertility preservation research, it would hold that it is just to offer young women and girls who may become infertile due to cancer treatments the opportunity to participate in investigational fertility preservation research. Participation in investigational fertility preservation research, as opposed to utilizing the more established method of embryo cryopreservation, is especially justifiable if the woman or girl does not have a partner, if she would prefer not to use donor sperm to create embryos for cryopreservation, or if she does not have time to participate in IVF before commencing cancer treatment [4, 26, 28]. As feminist theorist Karey Harwood has argued, participation in investigational fertility preservation research "is more justifiable if it is the patient's last best hope to preserve normal biological function in the face of a serious illness such as cancer," [23, p. 43] and in light of the abovementioned constraints this "last best hope" makes her more likely to personally benefit from the improvement of investigational fertility preservation techniques.

Despite the appropriateness of participation by the cancer patient population in research due to the potential personal benefit, concerns have been raised about the potential vulnerabilities that this population might face. In the case of oocyte cryopreservation these concerns include delay of cancer treatment and the introduction of ovarian stimulation hormones to mature oocytes in vivo, which may exacerbate estrogen-sensitive tumors [28]. Others have raised the concern that inadequate knowledge creates the opportunity for unjustified optimism regarding outcomes of participation in clinical fertility preservation research involving investigational methods [23]. Even when the risks and limitations of experimental research are fully explained to patients, there is a possibility that participants make have a high degree of hope that they will survive the cancer and that the fertility preservation technique will work for them [6, 24, 29]. As Inmaculada de Melo-Martin and Ina N. Cholst have argued, "evidence suggests that, although some people cite altruistic motives as their reason to participate in clinical trials, self-interest – in particular, they hope to benefit from the research – is more commonly given as a reason for participating in trials" [28, p. 526]. This perception of therapeutic benefit associated with participation in investigational research may raise the potential for false hope both for fertility preservation and for cancer treatment [23, 29], but as Zoloth has argued, it would be inaccurate to characterize this as therapeutic misconception because there is a real possibility for potential personal benefit to be gained from participation in investigational fertility preservation research (Chapter 24 by Zoloth, this volume). Clearly cancer patients' participation in fertility preservation protocols is not simply a case of altruistically motivated participation in research to advance medical knowledge if they themselves could benefit directly from the research. Striking the balance between patients' reproductive autonomy and appropriate research subject selection requires careful attention on the part of researchers recruiting participants for both basic and clinical research. Despite the fact that cancer patients are in the position to benefit most from the outcomes of research, they are vulnerable to the possibility of presuming there is a therapeutic benefit to participation in research even if the technique is still investigational. This is particularly relevant as the available investigational techniques are at different stages of technical maturity and have differential live birth rates. For instance, human live births have resulted from both oocyte cryopreservation and ovarian tissue transplantation while as of yet there have been no human live births with the use of in vitro follicle maturation techniques.

In addition, at this time little is known about long-term viability of cryopreserved human oocytes and ovarian tissue, the efficacy of using these fertility preservation techniques, and long-term health risks associated with these techniques [23, 30]. The model of enrolling those most likely to benefit from both clinical and basic research has been employed in the development of other forms of ART, but one danger of this precedent has been that investigational techniques have often moved into clinical use in the private medical sector with professionally generated practice guidelines instead of using a model of controlled clinical trials [24]. Thus it will be particularly important for clinicians and basic researchers involved in enrolling cancer patients in their investigational research protocols to ensure that these techniques are monitored for safety, efficacy, and long-term health outcomes of participants and any resulting children before they are deemed established methods in the realm of fertility preservation.

## *Fertility Patients*

For many women seeking fertility treatment, the goal of having a genetically related child is paramount. Women experiencing infertility may benefit from investigational fertility preservation research since it may offer more reproductive options to women who are seeking assistance with conception. Facilitating patients' reproductive choices has been a primary goal of assisted reproductive medicine in the United States (US), but it is important to assess whether and how fertility patients' reproductive autonomy is preserved and/or compromised through participation in investigational fertility preservation research. The ethical permissibility of participation in elective oocyte or ovarian tissue cryopreservation – both investigational techniques – to delay childbearing for social or lifestyle reasons has been addressed extensively in the literature [23, 28, 31, 32]. Thus rather than reiterating the debate on fertility preservation for lifestyle reasons here, my analysis will focus on women currently seeking treatment for infertility.

The ASRM has issued guidelines indicating that if IVF patients have oocytes that they are not going to utilize for their own fertility treatments, it is acceptable for these tissues to be donated for research provided that the patients undergo informed consent, that the decision to donate oocytes to research is not coerced, that the decision is separate from the decision to continue or terminate fertility treatment, and that patients are aware that they will not personally benefit from the outcome of the basic research [33]. Basic fertility research has relied on the donation of oocytes from IVF patients to improve upon oocyte cryopreservation and in vitro oocyte maturation techniques [34, 35], and following Ballantyne and de Lacey's framework, the participation of this population in basic fertility preservation research is justified since the population experiencing infertility stands to benefit from fertility-related research. However, due to the reality that fertility patients may have age-related diminished ovarian reserve and the immediacy of the fertility problems that women seeking fertility treatments are facing, it would be unjust to solicit the participation of IVF patients for basic ovarian tissue cryopreservation research because they themselves could experience more harm than benefit to their reproductive health and reproductive goals from removal of ovarian tissue for basic research purposes.

As for clinical research, the question remains as to whether it would be just to enroll women currently seeking fertility treatments in investigational fertility preservation research protocols such as oocyte or ovarian tissue cryopreservation. These investigational fertility preservation techniques are designed with the idea that a woman or girl's reproductive genetic material may be cryopreserved for use at a future date, while fertility patients may already be embroiled in the physical and emotional rigors seeking more immediate resolution to their fertility problems with ART. Given these temporal constraints and the immediacy of fertility patients' desires to build a family, de Melo-Martin and Cholst have argued that it would be more appropriate to utilize established fertility treatment protocols with this population because these women may already have compromised fertility and more established methods of fertility treatment would be more likely to help them to achieve their goal of having a baby than would an investigational technique [28]. However, they have also argued that it would be just to enroll current fertility patients in investigational research on fertility techniques only if other more established options had been excluded for moral, religious, or logistical reasons [28]. This option might be particularly relevant for women who are opposed to the creation and cryopreservation of embryos for future use, but would be willing to participate in ovarian stimulation and oocyte harvesting with the intention of only fertilizing the number of oocytes that could be transferred for pregnancy at one time or if they would be willing to use cryopreserved donor oocytes for their own fertility treatments [28].

Despite the fact that fertility patients as a population may benefit from the eventual maturation of cryopreservation techniques for oocytes and ovarian tissue, due to the immediacy of fertility patients' desires to conceive and have a baby, this is not the ideal population for participation in clinical fertility preservation research. Direct benefit may be less likely and could raise the potential for eliciting false hope for its immediate success. Despite any moral ambivalence that feminists may have regarding ART, it is ethically imperative that women who are willing to undergo the physical and emotional burdens of fertility treatment be best positioned to benefit from their efforts. However, investigational fertility preservation research is not necessarily the most well matched to achieving their reproductive goals at the present time.

## *Reproductive Oocyte Donors*

It has also been suggested in the scientific and bioethics literatures that women already donating oocytes for reproductive purposes might be an appropriate population to donate oocytes for basic and clinical fertility preservation research [28, 36]. While the Centers for Disease Control and Prevention reported that donor oocytes were used in approximately 13.7% of all IVF cycles in the US in 2005 (14,646 cycles overall) [37], egg-sharing arrangements, which are characterized by the donation of some of the oocytes from a donation cycle to researchers are not common in the US. In the United Kingdom, the Human Fertilisation and Embryology Authority allows IVF patients to enter into egg sharing for research purposes [38], but in the US women who are providing oocytes for another woman to use to try to have a baby are not typically involved in egg sharing with researchers.

While not uncontroversial, women who are reproductive oocyte donors have already taken on the risks associated with ovarian stimulation and oocyte harvesting to donate oocytes for reproductive purposes. Given that they have already undertaken the risks associated with oocyte donation, these women may be an appropriate population to provide oocytes for fertility-related research even if they themselves would not personally benefit from fertility preservation research [28]. However, because they will not benefit directly from fertility preservation research, egg sharers would be more appropriately categorized as healthy research volunteers. Applying Ballantyne and de Lacey's framework of just selection of research participants, it would be just to enroll egg sharers in basic fertility preservation research if they provide informed consent and they are adequately compensated for the direct and indirect costs associated with their participation in the research.

At face value this may seem straightforward. However, there are potential pitfalls associated with the informed consent process, knowledge of disposition of oocytes and the potential for commodification when enrolling egg sharers as healthy research volunteers. While it is standard practice for oocyte donors to relinquish property rights to their oocytes once they have provided informed consent for their extraction and donation [17], consent forms for reproductive oocyte donation have not always disclosed that donated oocytes and embryos resulting from the donated oocytes might also be frozen, discarded, or donated for research or to another couple for fertility treatments [39]. Previous research involving reproductive oocyte donors indicates that donors may have varying degrees of comfort with donating their oocytes for research purposes [40, 41], thus it is especially important to ensure that women considering egg sharing arrangements are apprised of the nature of fertility preservation research in the informed consent process. Similarly to IVF patients donating oocytes to research, it is important that egg sharers provide adequate informed consent for their participation in investigational fertility preservation research and that their decision is not make under undue influence [33]. In addition, applying Waldby's concerns regarding stratified oocyte markets to the context of fertility preservation research [19], the potential for exploitative commodification of oocytes in egg sharing arrangements runs high, particularly if they result in differential compensation for oocytes than reproductive oocyte donation or donation of oocytes specifically for research. While egg sharing arrangements for research may be justified under specific guidelines for informed consent and compensation, there is potential that this population may face similar risks to their health and commodification or exploitation of their reproductive resources as the population of healthy research volunteers discussed below.

## *Healthy Research Volunteers*

The final category to consider for participation in investigational fertility preservation research is the population of healthy research volunteers. This population consists of healthy women willing to provide oocytes and ovarian tissue expressly for basic fertility preservation research. These individuals do not stand to benefit directly from the knowledge generated from investigational fertility preservation techniques, therefore according to Ballantyne and de Lacey's framework for just selection of research participants, just participation would necessitate the provision of informed consent and compensation for the direct and indirect costs associated with participation.

Ballantyne and de Lacey assert that adequate compensation for involvement in research can help avoid exploitation of healthy research volunteers, but the potential for exploitation still exists, particularly when differential compensation schemes and volunteers' long-term health are considered. The solicitation of healthy research volunteers to provide oocytes for stem cell research can serve as an instructive model for the fertility preservation research context. In the US context the stem cell community has solicited healthy young women to donate oocytes specifically for research purposes, but leading stem cell researchers have been unsuccessful in their efforts due to inadequate compensation schemes for research volunteers [42]. However, private oocyte donation companies and New York State's new allowance for financial compensation for oocyte donation specifically for research may offer the opportunity to assess women's willingness to participate when both direct and indirect costs are covered at rates comparable to women providing oocytes for reproductive purposes [19, 43]. Researchers' experience of offering inadequate compensation to prospective donors suggests that compensation is an important factor in the decision-making process for prospective healthy research volunteers for stem cell research which would imply that the same may be true for fertility preservation research volunteers. Given the importance of compensation for participation in research, it is important to raise Waldby's concern that stratified payment for reproductive tissues exacerbates the potential for exploitation of poor women seeking to reap financial rewards for providing their scarce reproductive resources to researchers [19]. Should fertility preservation researchers seek healthy research volunteers to provide oocytes and ovarian tissue, guidelines would be needed to ensure measures for achieving fair compensation without financial exploitation.

Another population of healthy research volunteers who may provide oocytes or ovarian tissue for fertility preservation research would be women undergoing voluntary sterilization [31] or who have had undergone elective oophorectomy for other medical reasons [25]. These populations have donated reproductive tissues for other types of fertility-related research [44], thus it may be appropriate to involve their participation in fertility preservation research. However, the decision to undergo sterilization or have an ovary removed would necessarily need to be separated from the decision to donate oocytes or ovarian tissue for fertility preservation research, and undue inducement in the form of financial or other compensation would need to be prohibited. Careful consideration is needed to establish protocols for adequate compensation in relation to related risks of participation for this population.

The main vulnerability that the participation of healthy research volunteers elicits is related to the long-term health implications of ovarian stimulation and ovarian tissue removal. Ovarian tissue removal and oophorectomy have well-characterized risks related to undergoing a surgical procedure as well as reproductive health risks such as surgical menopause [45]. And although there has been speculation on links between ovarian stimulation and long-term health risks like ovarian, endometrial, and breast cancers, ovarian cysts, fibroids, thyroid disorders, and pelvic pain, the results of existing research has been inconsistent in drawing causal links between ovarian stimulation and these health risks [46–49]. Given the particular commitment of oncofertility research to protecting the reproductive potential of cancer patients, additional research is indicated to assess the long-term health risks of oocyte donation and ovarian tissue donation both for reproductive and research purposes. Presently it is unknown whether the involvement of healthy research volunteers in fertility preservation research may put volunteers' own fertility and reproductive health at risk. For this reason, it would be advisable to focus investigational fertility preservation research on populations most likely to benefit from the clinical outcomes of research rather than to jeopardize healthy research volunteers' reproductive health.

## Conclusions and Directions for Future Research

While there are potential pitfalls associated with each of these prospective research populations, cancer patients are the most appropriate population to participate in both basic and clinical investigational fertility preservation research because they are most likely population to benefit from the establishment of these methods in clinical care. Fertility patients, reproductive oocyte donors, and healthy research volunteers may be suitable research subject populations for the basic research associated with investigational fertility preservation techniques under certain circumstances, but the potential risks to their own reproductive health and the potential for commodification of their reproductive tissues make these populations more vulnerable as research subject populations than women facing fertility-limiting cancer treatments. Hence, women whose cancer treatments are likely to adversely affect their fertility should be the primary population recruited for participation in investigational fertility preservation research.

Finally, while facilitating patients' reproductive autonomy is paramount, it is important to raise the longstanding feminist question regarding ART of whether the existence of investigational fertility preservation techniques raises the technological imperative to participate [9, 11–15]. Querying which cancer patients will be most likely to participate in investigational fertility preservation research, and if and how the decision to participate relates to a cultural norm of achieving womanhood through biological motherhood will be important directions for future research. To this end, adequate assessment of the ethical implications of investigational fertility preservation protocols should include the perspectives of those women and girls who have considered and participated in investigation fertility preservation research. At this time little is known about patient receptiveness and enthusiasm for various fertility preservation methods and what factors impact patients' decisions to choose an established method, an investigational method of fertility preservation or to forego fertility preservation with ART. Results from a preliminary study reviewing cancer patients' charts in a fertility preservation program revealed that more patients opted for the established method of embryo cryopreservation or opted out of

ART-assisted fertility preservation altogether than chose either oocyte cryopreservation or ovarian tissue cryopreservation [25]. Hence, it is important to systematically track cancer patients' motivations for choosing specific fertility preservation techniques and their attitudes about use of reproductive tissues in basic fertility preservation research, as well as to include long-term follow up with women and girls who opt in and opt out of fertility preservation research. Further exploration of the experience of participation in fertility preservation research will provide important insight into the worldviews and moral frameworks of those poised to benefit from investigational fertility preservation techniques, which will in turn provide firmer ground for empirical bioethical analysis of the risks and benefits of participation in investigational research.

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# Chapter 17
# Reproductive ‘Choice’ and Egg Freezing

**Angel Petropanagos**

> *Of course some women, for various reasons, choose to embrace motherhood later than their own mothers. But many, like me, become older mothers because there was no other choice. It’s just how my life unfolded. . . . To suggest that most women are choosing to delay child-bearing is to suggest that women have an incredible level of control over their lives. In the real world this is just not true.*
>
> – Sushi Das [1]

## Introduction

As oocyte and ovarian tissue cryopreservation techniques continue to improve [2, 3], there is a growing need to address the moral permissibility of what has been called ‘social’ egg freezing.[1] Often used to preserve the fertility of cancer patients, egg freezing has recently gained popularity among women wishing to guard themselves against age-related infertility. Higher education, career advancement, an increased cost of living and difficulties finding a long-term partner are just some of the reasons why a number of women are having children at an older age [4, 5]. Delayed attempts at childbearing[2] can present obstacles for women wishing to bear their

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[1] In this chapter I shall use the term ‘egg freezing’ to refer to the initial and subsequent phases of fertility preservation methods for women. These include the initial removal and cryopreservation of oocytes, ovaries and ovarian tissue as well as the subsequent in vitro maturation of immature oocytes, in vitro fertilization and ovarian transposition.

[2] Although, the phrase ‘delayed attempts at childbearing’ can describe a women’s attempt to conceive and have children at an older reproductive age, it should be noted the phrase is problematic because it can imply that women who have (or attempt to have) children when they are older do so ‘voluntarily’. As I will argue in this chapter, the ‘choice’ to delay childbearing may not be fully voluntary.

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own biological children because fertility declines with age due to a reduced number and quality of oocytes [6]. Egg freezing allows a woman to freeze her own younger and healthier eggs for future use in the event that she is unable to conceive a child ‘naturally’.

Recent debates in the media and elsewhere have employed the terms ‘medical’ and ‘social’ to distinguish between two prevalent reasons for freezing eggs. Medical egg freezing describes the use of egg freezing technology by women who are diagnosed with cancer or other serious disease whose treatment and/or progression can damage reproductive organs.[3] The term ‘medical’ highlights the fact that women who use this service are choosing to do so (in part) because of a medical condition or disease that threatens to destroy their genetic reproductive capacities. Social egg freezing, on the other hand, describes the use of egg freezing technology by *all other* women. The term ‘social’ has been less problematic than some other terms used in the media such as ‘lifestyle’ reasons, which risk exaggerating the level of reproductive control some women actually have. Indeed, perhaps this term may help to accentuate the fact that women’s reproductive choices are socially embedded and cannot be understood in isolation from the social context in which these choices are made. However, the same would also apply to women who use the technology for medical reasons. Calling some uses of egg freezing ‘social’ is somewhat problematic because it downplays the importance of having genuine reproductive options in one’s life. This term can also suggest that if these women have a ‘social’ problem, then it requires a ‘social’ solution rather than a ‘medical’ one such as egg freezing. Medical reasons, on the other hand, apply to both types of egg freezing if we accept that infertility is a medical condition or disease (although it is open to debate as to whether age-related infertility should be classified as a disease [7]). It follows from these considerations that the demarcation between social and medical reasons for freezing eggs becomes quite complicated once we recognize that *both* sorts of reasons will factor into *all* women’s deliberation about fertility preservation.

Rather than continue to use terms that may be problematic and value-laden, I will refer to the medical cases as *the use of egg freezing to guard against disease-related infertility* and call this practice as *disease-related* egg freezing; and I will refer to the social cases as *the use of egg freezing to guard against age-related infertility*[4] [8] and call this practice as *age-related* egg freezing. I believe doing so will avoid many of the problems I have mentioned.

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[3] For example, bone marrow or stem cell transplantations, oophorectomy for cancer prophylaxis or benign conditions can threaten women’s fertility. Certain autoimmune and rheumatological conditions can also lead to infertility.

[4] Karey Harwood describes social egg freezing as ‘insurance against age-related infertility’. My use of ‘age-related’ infertility thus picks up on Harwood’s description, but avoid the assumption that egg freezing is ‘insurance’ that guarantees successful pregnancies when frozen eggs are thawed and used in the future.

Despite recent advancements in egg freezing, a number of regulatory bodies and individuals continue to voice concern over the safety and success of this reproductive technology when used to guard against age-related infertility. For example, the American Society for Reproductive Medicine (ASRM) continues to discourage physicians from marketing egg freezing to women as a means of deferring reproductive aging [9]. The ASRM recognizes that many women have an interest in this technology, but maintains that egg freezing is still an 'experimental' [10] procedure that should only be used for medical reasons.[5] Others who object to age-related egg freezing have labelled it an 'expensive confidence trick' [11] and a 'contestable form of wishful medicine', [12] while at the same time praising disease-related egg freezing for giving women with cancer hope and future reproductive options [13]. These individuals suggest that the health risks to women and/or future offspring and the risk of 'false hope' are reasons to restrict age-related egg freezing. They claim that instead, women ought to have children at a younger age [14] or simply 'live with their life choices'. [12] Although some of these concerns about the risks associated with egg freezing may be legitimate, it is not clear whether a strict ban on age-related egg freezing is morally justified, given that disease-related egg freezing is permitted.

Admittedly, there are serious moral concerns about the long-term safety, efficiency and social impact of the procedure of egg freezing in general. These concerns raise the question of whether egg freezing ought to be allowed for any woman, whether her reasons are disease or age related; however, answering this question is beyond the scope of my chapter. Instead, the task of this chapter is to examine whether there are any moral grounds to restrict egg freezing for age-related reasons while allowing egg freezing for disease-related reasons. I begin my analysis by considering the similarities between women who freeze eggs for disease-related reasons and those who freeze eggs for age-related reasons. I then consider some differences between each group of women by considering Imogen Goold and Julian Savulescu's [15] examination of the *timing* and the *cause* of women's infertility. The authors suggest that neither of these differences is morally relevant and argue in favor of women's access to age-related egg freezing. However, I suspect those who continue to object to age-related egg freezing will be unconvinced by Goold and Savulescu's analysis of the temporal and causal differences in infertility. I spell out these objections to Goold and Savulescu and maintain that their analysis fails to address the underlying concerns about age-related egg freezing. I argue that objectors to age-related egg freezing who think the differences in timing and/or cause *are* relevant are ultimately relying on a mistaken understanding of women's reproductive 'choices'. Using a feminist analysis of the notion of 'choice', I show that the differences between disease and age-related egg freezing continue to bear little

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[5] The ASRM defines experiments as 'a procedure for the treatment of infertility is considered experimental until there is adequate scientific evidence of safety and efficacy from appropriately designed, peer-reviewed, published studies by different investigator groups'. Until there is 'adequate peer-reviewed scientific evidence', egg freezing will be considered an 'experimental' procedure regardless of improved rates of success in clinical trials and fertility clinics.

moral relevance. I argue that if egg freezing is permitted to guard against disease-related infertility, then it ought to also be permitted to guard against age-related infertility, (at least) within a patriarchal society.

## Disease-Related Versus Age-Related Egg Freezing

There are a number of similarities between women who freeze eggs for disease-related reasons and those who do so for age-related reasons. First, women in both groups are fertile when they have eggs or tissue removed for cryopreservation and storage. Thus the initial phase in the egg freezing procedure is guarding against a problem that has not yet occurred, namely infertility. When frozen and stored eggs or tissue is used in the future it is likely that the women in each group will be infertile whether this is because of treatment for a disease or because of their age.

Second, women in each group share common motives for undergoing the treatment. Women who face infertility because of a disease treatment or progression are using egg freezing technology with the hope of securing their future reproductive options. Likewise, women who freeze eggs to guard against age-related infertility are concerned about preserving their future reproductive options. Both groups of women want to have the option to use their own (younger, healthier) eggs to try and conceive if attempts at unassisted, natural conception are unsuccessful. Women in each group treat egg freezing as a form of insurance guarding them against future infertility, regardless of their awareness of the chance that egg freezing may not be successful in all cases. Yet, egg freezing is intended as a ‘back-up plan’ or ‘last resort’ in the event that natural conception fails.

Third, it follows that the women in each group experience similar benefits from using egg freezing technology. Cancer, among other diseases, can bring suffering to patients (and families) and egg freezing can help lessen some of this present and future suffering. Egg freezing can relieve some of the worries associated with cancer and can give women a sense of empowerment since they are making the choice to try and protect themselves from infertility. It has also been suggested that for some women, infertility can be as devastating as the cancer diagnosis [16, 17]. Likewise, many of the hardships that lead women down paths that delay motherhood can also be quite difficult in their own right. Making egg freezing options available to these women can help alleviate some of the financial pressure of trying to have a family at a young age, the emotional stress of finding ‘Mr. Right’ or the guilt and anxiety experienced when having to choose between a higher education and a career versus starting a family. For any young woman who finds herself unable to satisfy a desire to bear children at present, egg freezing can help lessen her anxiety about reproducing by offering her some security (or increased hope) for the future and for giving her some level of reproductive control. Infertility can be devastating for any woman who wishes to reproduce genetically but cannot.

Fourth, women in both groups are affected by the risks associated with egg freezing. These risks include ovarian hyperstimulation syndrome (OHSS) [18], low success rates [19],[6] risk to future offspring [9][7] [20, 21] and also the devastation and sense of loss if the future fertility treatment is not successful. Although these risks do exist, there is evidence suggesting that the risk may be higher for women with cancer or other diseases compared to the risk for healthy women who use the procedure to guard against age-related infertility. Women with cancer might face higher risks because egg freezing requires a delay in starting the chemotherapy or radiation necessary to treat their cancer. There is also a risk of reintroducing cancerous cells into the women's body upon future use of the oocytes or ovarian tissue [22]. Other similarities between each group include the devastation caused by infertility to those women who wish to have a biological child and the possibility of dealing with financial, legal and ethical issues surrounding storage and disposal of unused frozen eggs.

These similarities suggest that most women who freeze eggs experience the same benefits and harms associated with the reproductive technologies. In the next section, I present two major differences between disease-related and age-related egg freezing, as discussed by Goold and Savulescu, and explain why they consider neither difference to be morally relevant.

## Goold and Savulescu on *Timing* and *Cause*

In 'In Favour of Egg Freezing for Non-medical Reasons', Goold and Savulescu present arguments based on equal concern and respect for women that suggest women should have access to ovarian tissue and oocyte cryopreservation. They claim that provided women are fully informed and prepared to deal with the 'failure of their insurance policy', women should not be restricted from freezing their eggs because they are outside medical treatment for cancer or another disease. In their analysis, Goold and Savulescu suggest that the *timing* of the infertility and the *cause* of the infertility are the two main differences between women who freeze eggs for disease-related and age-related reasons.

The authors notice that women who freeze eggs for disease-related reasons usually become infertile quickly or immediately after their cancer treatment begins,

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[6] The success of egg freezing technology varies with respect to the specific procedure being offered (including the processes by which eggs are frozen and thawed, the method/site of re-implantation) and also the relevant features of the patient (such as age and health). Many people worry that because using egg freezing technology to reproduce is less certain than using 'natural' conception within the optimal reproductive age (20–35), women (and couples) risk being exploited by fertility clinics and risk developing 'false hope' concerning the procedure's success.

[7] Although the ASRM warns women that there is a risk to future offspring due to the effects of cryopreservation on meiotic spindle of the oocyte, there remain concerns regarding the potential for chromosomal aneuploidy or other karyotypic abnormalities in offspring; some studies have suggested that oocyte cryopreservation produces risks to offspring that are actually comparable to 'natural' conception. However, given the experimental nature of female fertility preservation techniques, the risks are largely unknown.

while those who freeze their eggs for age-related reasons usually experience infertility in the more distant future. Some women with cancer, for example, will face nearly certain and imminent infertility at the onset of their chemotherapy or radiation. Women who freeze their eggs for age-related reasons cannot be quite as sure about when they will experience infertility, but in most cases these women can expect to become infertile in the more distant future. Many of these women can expect, however, that there fertility will rapidly decline around 35 years of age. The authors suggest that according to the principle of temporal neutrality the timing of this harm (infertility) makes no moral difference [15, p. 43]. The principle of temporal neutrality states that the temporal location of benefits and harms within a life has no normative significance. As such, the timing of a harm (or benefit) is independent of any analysis of an agents overall well-being. This means that the time at which a woman becomes infertile ought to be given no moral weight in the moral evaluation of her choice to use egg freezing technology. In other words, a woman who freezes her eggs in order to guard against infertility that will occur in 2 months time is no different morally speaking than a women who freezes her eggs in order to guard against infertility that will occur in 10 years time.

Goold and Savulescu also claim that the *cause* of the infertility makes no moral difference between disease-related and age-related egg freezing. In the case of women who freeze eggs for disease-related reasons, medical intervention to treat her disease is usually the cause of her infertility. In the case of women who freeze eggs for age-related reasons, the authors identify menopause as the cause of her infertility. The authors claim that it is morally irrelevant that the cause is menopause rather than chemotherapy to treat cancer [15, p. 52]. They suggest that the cause of infertility makes no moral difference because the loss experienced by women who are infertile but wish to have their own biological children is the same.

Although Goold and Savulescu have identified what are probably the two best candidates for the morally relevant differences between disease-related and age-related egg freezing, I believe that their examination of these differences and subsequent dismissal of their moral relevance are rather quick. In the next section I consider objections against age-related egg freezing that requires a broader or perhaps different understanding of timing and cause.

## Objections to Goold and Savulescu

Many objections to age-related egg freezing are masked as legitimate worries about the associated risks with this reproductive technology and, surprisingly, objectors find these risks more worrisome for healthy women seeking to guard themselves against age-related fertility than for women already more vulnerable and sick with cancer or another disease. For example, the ASRM advocates egg freezing to guard against disease-related infertility, but discourages women for freezing eggs to guard against age-related infertility because the procedure is ‘risky’ and ‘experimental’, and calls women with cancer or other illness ‘appropriate candidates’ for egg freezing since they may have 'no viable options' [23]. Some regulating bodies, like the ASRM, have resisted policy revisions despite research suggesting the improved safety and success of egg freezing technologies. It may be the case that what seems to be a paternalistic policy against age-related egg freezing is actually masking unjustified assumptions or biases of persons serving on regulatory bodies. One such assumption may be the belief that women who use age-related egg freezing have more (or better) options than those who use disease-related egg freezing. In what follows, I consider what grounds this assumption and why it is problematic.

I suggest that those who object to age-related egg freezing, but accept disease-related egg freezing understand the concepts of 'timing' and 'cause' quite differently than presented by Goold and Savulescu. As I discussed in the previous section the authors take timing to refer to the *time at which a woman becomes infertile*. They note that women who use egg freezing for disease-related reasons experience infertility in the very near future, but women who use age-related egg freezing experience infertility in the more distant future. Objectors understand this temporal difference to signify that there is a relevant difference in the 'opportunity' afforded to women in each group. One might argue that women who freeze eggs for age-related reasons still have the opportunity to 'fix' the problem of infertility. For example, a woman who decides to freeze eggs in her mid-twenties still has approximately a decade to have children before she becomes infertile because of her age. Thus, she can 'fix' the harm before it occurs. On the other hand, a woman who freezes her eggs for disease-related reasons does not usually have this same window of opportunity since her infertility happens almost immediately. A woman with a life threatening cancer diagnosis cannot delay chemotherapy or radiation for 9 months to have a child before her fertility is compromised, but objectors would argue a healthy woman can have children before she is too old to conceive naturally. A woman who freezes her eggs for age-related reasons has the opportunity to prevent the potential problem of infertility, while a woman who freezes her eggs for disease-related reasons does not.

One might also object to what Goold and Savulescu identify as the cause of infertility, despite admitting that the loss associated with infertility can be the same for women in each group. According to the authors, menopause is the cause of women's infertility.[8] Menopause is often understood as a biological happening which is beyond a woman's control. Believing that the cause of infertility *is* morally relevant requires thinking about cause in a different way. Objectors recognize that the infertility of women in treatment for cancer is iatrogenic, i.e. physician caused. On the contrary, the infertility of women who freeze for age-related reasons in non-iatrogenic. In the first group, the physician's treatment of the woman's disease is causally responsibility for the infertility. However, in the case of age-related egg freezing the woman who voluntarily waits to bear children until after menopause is the cause *herself*. According to the objectors, a woman's actions (or lack thereof)

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[8] The use of the term menopause might be slightly misleading since female fertility begins to decline many years prior to the onset of menopause despite continued regular ovulatory cycles. Although there is no strict definition of advanced reproductive age in women, infertility becomes more pronounced after the age of 35.

that result in her delayed attempts at bearing children makes the woman *herself* morally responsible for the infertility. Here, objectors assume that causal responsibility is linked to moral responsibility and understand women who freeze eggs for age-related reasons as voluntarily choosing to delay motherhood.

The force behind these two objections lies in the argument that women who freeze eggs for age-related reasons could choose to do otherwise. Both these objections highlight an underlying worry about the role that women's choices play in relation to the use of reproductive technologies, like egg freezing. Notably, the ASRM's policy on egg freezing mentions that disease-related egg freezing is permissible because these women have 'no other choice' [23]. This implies that women who choose to undergo age-related egg freezing do have other options. It is assumed that women who freeze eggs for age-related reasons are choosing to put motherhood on hold for selfish reasons like pursuing higher education or advancing a career.

Unlike Goold and Savulescu, these objectors assume that the choices women make ought to be included in the causal differences between disease-related and age-related infertility. Given the opportunity to fix the problem and the voluntariness of delaying childbearing, objectors hold that women outside of medical treatment are different than woman undergoing treatment because they choose to delay childbearing and subject themselves to the risks associated with egg freezing. In the next section I explore this notion of 'choice' in relation to moral responsibility within the context of patriarchy.

## Why the 'Problem' is Not So Easy to Fix and the 'Choice' is Not So Voluntary

The above objections rely on an arguably sexist and false conception of an agent's autonomy. The claim that women could just fix the problem and that they could simply choose to do otherwise boast ignorance of the social structures that shape, confine and influence the choices women make. Feminist accounts of autonomy and the nature of choice pay special attention to the patriarchal context in which autonomy is exercised and choices are shaped. Carolyn McLeod and Susan Sherwin, for example [24], argue that in addition to coercion, ignorance and internal compulsion, forces of oppression can also compromise an agent's autonomy. Unlike traditional accounts of autonomy, feminists' accounts of autonomy require an explicit recognition of the fact that autonomy is both defined and pursued in a social context. Further, this social context significantly influences the opportunities that an agent has to develop or express autonomy skills. McLeod and Sherwin suggest that 'whereas traditional accounts concern themselves only with judging the ability of the individual to act autonomously in the situation at hand, relational autonomy asks us to take into account the impact of social and political structures, especially sexism and other forms of oppression, on the lives and opportunities of individuals' [24, p. 260). Relational autonomy requires that one looks at the various and complex circumstances that surround an agent's decision-making process. In the context of age-related egg freezing, a relational approach to autonomy requires one to understand the personal, social and political factors that shape women’s reproductive choices. Using a feminist analysis of choice, I shall demonstrate why these broader or different notions of timing and cause are still not morally relevant.

In the first place, there are reasons to believe that the problem women face is not really that easy to fix. Many women may like to have children before the onset of age-related infertility, but have been unable to find a suitable or willing long-term partner to have children with. Single women nearing their mid-thirties (or older) usually have a very small window of opportunity to meet someone and begin the process of becoming pregnant before they suffer from infertility. Just like women who freeze eggs for disease-related reasons, women nearing the end of their reproductive fertility may have few or no other options to secure having their own biological children in the future. Women who wish to have their own biological children currently have two options aside from age-related egg freezing to reach their goal. They can quickly settle for a partner who they might not have chosen otherwise or they can use donor sperm and choose to be a single parent. From a feminist perspective, neither of these alternatives is ideal.

Rushing into a relationship can make it difficult for women to recognize physically or emotionally abusive partners. Feminists would agree the women should not have to settle for men who reinforce sexists and oppressive family structures. Instead, women should have the opportunity to find a stable, reliable and loving partner with whom they want to build a family. However, it takes time to find a suitable partner, develop a relationship and start a family. If women rush to have biological children, they may also opt for single parenthood. Many feminists recognize that raising children is a difficult job and single parenthood can be particularly challenging for those of lower economic status. Age-related egg freezing may give women the opportunity to find a suitable partner or gain some financial independence before tackling single parenthood.

There are also couple of additional points worth making here. First, there are a number of social norms and ideals that favour the nuclear family structure and discriminate against diversions from this norm. The nuclear family requires a marriage between a man and a woman and striving for this ideal can delay when women have children. There is also a social bias towards biological parenthood. Women who internalize these social norms might refuse other reproductive options such as sperm or egg donation, surrogacy and adoption. Indeed, some studies suggest that conformity to traditional gender roles within a partnership or marriage can impact women’s and couples’ decisions to bear children [25]. Second, women’s choices to delay motherhood have almost always been at the centre of discussions around delayed parenthood and age-related egg freezing. The reproductive and ‘lifestyle’ choices made by men have generally been neglected. If men are reluctant to commit to long-term partnerships or choose to have children at a younger age, this can impact the childbearing decisions made by women. It is important to consider the effect that men’s reproductive choices have on the growing trend towards age-related egg freezing. Goold and Savulescu claim that ‘where egg freezing could offset the problem associated with this particular trend of a difficulty in conceiving, there is good reason to allow the technology to be used' [15, p. 57). Thus, egg freezing might help address some reasons that might otherwise lead some women into unhappy marriages, single parenthood or unwanted childlessness. Finally, since men have been able to freeze sperm for decades, one might think that egg freezing is an important tool for ensuring gender equality.

Just as the problem is not so easy to fix the choice to delay motherhood is not so voluntary. An objector who employs an expanded notion of cause to include the woman *herself* as a cause of delayed motherhood and subsequent age-related infertility. This objector might argue that if a woman delays attempts at bearing children until she is older, then she must accept responsibility for (and thus the outcome of) her actions. This suggests that it is the woman's fault that she is infertile and not merely the consequence of an external event (such as cancer). Highlighting such causal responsibility seems to also imply a belief that the woman is also morally responsible. However, causal responsibility does not necessarily involve moral responsibility. For example, a woman can be causally responsible for opening a door to enter an office without being morally responsible if the door stubs a co-worker's toe. This may be because *no one* is *morally* responsible in this example because the event does not involve a moral issue. Or, the moral responsibility/blame lies elsewhere, such as the manufacturer who constructed a faulty door hinge that causes the door to swing open uncontrollably. In the case of a woman who plays a causal role in her infertility and childlessness, it may be the case that she is not morally responsible because infertility (or childlessness) is not a moral issue. Or, it might be the case that others are morally responsible for the woman's infertility. From a feminist perspective we can recognize that social structures, ideologies and norms shape and influence the options available to women and thus impact the decisions women make. This might mean that a patriarchal and sexist society patriarchy, everyone, or some persons in the privileged group are morally responsible for delayed attempts at parenthood.

Arguably, the objectors have failed to recognize the diverse set of obstacles that can impede a woman's ability to bear children at a younger age. These obstacles include financial barriers and the structure of academic institutions and employment. The cost of living has increased from decades past, and raising children can be financially challenging even in two-income households. Women or couples may choose to save money and gain financial stability before having children. Thus, bearing children at a younger age may risk pushing women or couples into poverty or a work schedule not conducive to raising children. The structure of education makes it quite difficult to care for young children while completing a degree. Many women may have to delay bearing children until after completing their degree in order to avoid the challenges women face in post-secondary programs. Finally, and perhaps most importantly, the employment system is not structured to support parents who maintain (or pursue) a career while they have young children [8]. Notably, employer policies can seriously influence women's reproductive decisions. Women who work in establishments or professions with family-friendly policies are more likely to have their preferred family size than women whose employment hinders their ability to raise children and have a career [26]. Patriarchy sets serious barriers to childbearing, and delaying reproduction might help some women manage or avoid sexist systemic barriers. Understanding how these factors can confine reproductive options and influence family planning suggests that the choice to delay childbearing is not nearly as voluntary as some objectors think. Just as the problem is not so easy to fix, the 'choice' to delay bearing children is not fully voluntary.

## Discussion and Conclusion

As I have already mentioned, objectors understand women's reproductive choices as autonomous in a way that is removed from the social context within which these decisions are ultimately embedded. However, the analysis of reproductive choice and egg freezing should begin from the social context within which it occurs. All women making reproductive choices are socially and historically situated, which ought to be taken into account when considering the moral permissibility of them using a particular reproductive technology. In particular, the context of patriarchy is integral in shaping women's reproductive choices. A deeper understanding of how oppression operates can illuminate the ways in which women's options and ultimate decisions are shaped by patriarchal social structures and ideologies.

The reproductive technology of egg freezing, however, cannot escape the serious feminist worry about potentially reinforcing patriarchy and leaving the problematic social structures largely intact. Karey Harwood, for example, argues that egg freezing as a guard against age-related infertility is just a 'quick fix' to balancing the opportunities available to men and women and leaves the problems rooted in gender inequalities largely untouched. Egg freezing can actually do more harm than good and ultimately threaten women's reproductive freedom by ignoring the social structures (like employment) that make it difficult for women to have a family and a successful career. Goold and Savulescu suggest that despite the need to alter our social structures, egg freezing can be helpful in the short term, provided we have the proper restrictions set in place for the use of this technology [15]. At the same time we offer age-related and disease-related egg freezing, we should introduce measures to try to fix the larger problems related to gender inequalities. Relational autonomy 'seeks politically aware solutions that endeavour to change social conditions and not just expand the options offered to agents'. [24] Thus, understanding women's reproductive choices within patriarchy can help highlight the areas of society that influence women's reproductive options. Accordingly, these areas of concern can be addressed as we work towards changing the underlying social structures that make childbearing difficult.

There are also some concerns about the general social norms that egg freezing might promote or create. Indeed, egg freezing might reinforce patriarchal norms. If egg freezing reinforces pronatalism and the expectation that childbearing is women's (primary) social role, then egg freezing might promote sexist social expectations and threaten women's autonomy [27]. Egg freezing might also uphold the biases towards biological parenthood and reinforce a stigma against adoptive parenthood. These concerns, however, are not reasons to ban age-related egg freezing if we continue to allow disease-related egg freezing. Further, the impact on individual women or women as a group might suggest ways in which egg freezing ought to be regulated or marketed to promote more positive social ideals and foster reproductive autonomy.

Although my analysis relies on the problems that arise when we assume women are fully in control of their reproductive choices, individual women have varying degrees of reproductive choice and control, even within patriarchy. Some women's reproductive choices will be freer than others. However, it is reasonable to generalize the problems with women's reproductive choices under patriarchy for the sake of developing public policies on egg freezing. Also, the arguments presented in this chapter are compatible with imposing regulations on both disease-related and age-related egg freezing intended to lessen some of the potential harms or broader social concerns.

In this chapter I have not taken a stance on the moral status of any woman's use of egg freezing technology. It might be the case that egg freezing is too risky for women or too harmful for the offspring born from frozen eggs. Rather, I have suggested that there are (at present) no morally relevant differences between women who freeze eggs to guard against disease-related infertility and those who freeze eggs to guard against age-related infertility. If we continue to allow disease-related egg freezing, then we ought to also allow age-related egg freezing, given the patriarchal context of women's reproductive choices. Until the sexist social structures that shape and confine women's reproductive choices change, many women may continue to find their lives unfolding in ways that result in delayed motherhood.

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# Chapter 18
# The Impact of Infertility: Why ART Should Be a Higher Priority for Women in the Global South

**Amanda Fleetwood and Lisa Campo-Engelstein**

## Introduction

Cancer is typically associated with countries in the global North[1] rather than the global South. This is in part because cancer is often portrayed as a disease of late middle to old age and the global North has a larger percentage of this particular demographic than the global South. Yet, cancer is the third leading non-communicable cause of death in developing countries [1]. Furthermore, the American Cancer Society estimates that over half of all new cancer cases were in the global South in 2007. Specifically, almost 3.6 million of the 6.6 million new male cancer cases worldwide and over 3.1 million of the 5.7 million new female cancer cases worldwide afflicted men and women in the global South [2]. As these numbers show cancer is not a disease only or mostly affecting people in the global North, it also affects a substantial population in the global South.

Many of the established treatments for cancer, like chemotherapy, radiation, and surgery, run the risk of infertility for both women and men. The social consequences of infertility for women in the global South are especially devastating, ranging anywhere from ostracism to spousal violence. Yet fertility preservation treatment for women with cancer in the global South is generally not available for a variety of reasons, most of which center around money. These resource-poor countries typically lack both qualified health-care professionals and facilities necessary for fertility preservation treatment and other assisted reproductive technologies (ART).

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[1] In this chapter we are using the term "global North" to refer to the collection of countries often classified as "developed" or "industrial." We are using the term "global South" to refer to the collection of countries generally labeled as "developing." We use these particular terms because the concept of development is complex and therefore it is difficult to come to agreement on what criteria make a country developed or developing. Additionally, the terms "developing" and "developed" not only imply that there is a linear path from the latter to the former but also that the latter is unequivocally better in most, if not all, ways. Though problematic, we will also use the more traditional terms "developing" countries and "developed" countries in this chapter.

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Although some countries do have ART centers, the cost of ART is prohibitive for all but the extremely wealthy. Indeed, infertility is usually seen as a treatable problem for the upper class primarily because the poor cannot afford basic health care let alone expensive treatment like ART [3, p. 32]. The fact that the majority of people in the global South cannot afford basic health care, which is typically seen as the top priority in health-care allocation, is another reason why ART are not readily available in the global South. Most public and private health-care funding goes toward primary care and not treatments that are often seen as elective and cosmetic, like ART.

While we agree that preventive and basic health care should remain the priority for countries in the global South, we also think the very low prioritization of ART, including fertility preservation treatment, should be reconsidered. Taking a feminist perspective, we argue that given the severe social, economic, and health-related consequences of infertility for women in the global South, ART should be more accessible and affordable. Given the large discussion this topic entails, we merely highlight and briefly provide some of the key points. Indeed, this chapter serves as an overview and in no way is it a fully articulated argument.

We divided this chapter into five sections. In the first section, we explain why a feminist approach is important when examining reproductive matters in the global South. In the second section, we discuss some of the adverse effects of infertility for women in various geographic regions of the global South. In the third section, we outline one of the most common objections to making ART a priority in the global South: that there are more pressing and important diseases to prioritize. We then provide three responses to this objection in the fourth section. First, we point out that ART need not be exorbitant. Second, we assert that as a matter of social justice, reproductive autonomy should include the right to have a child. Third, we argue that increasing women's autonomy, including their reproductive autonomy, is an important step in countries' economic development. In the fifth section, we return to the topic of women with cancer to show that fertility preservation treatment should be offered to this population because of the potential double burden they face as cancer and infertility patients.

## Why a Feminist Approach?

In analyzing infertility, ART, and women in the global South, we choose to employ a feminist approach because it acknowledges power structures and hence can uncover hidden gender inequities. In contrast, traditional ethical approaches often ignore or inaccurately portray the realities of life. Traditional ethics is frequently guilty of treating the public and private realms as two distinct spheres and often ignores the latter. In the words of Rosemarie Tong and Nancy Williams, "traditional ethics view as trivial the moral issues that arise in the so-called private world, the realm in which women do housework and take care of children, the infirm, and the elderly" [4, p. 1]. Reproduction and family matters are generally relegated to the private realm. It is therefore important to utilize a theory that not only recognizes the complex interplay between public and private realms, but also incorporates social context. A feminist approach allows us to reveal and critique oppressive practices because it includes social groups, not just individuals, in its examination. As Marilyn Frye persuasively argues, oppression is based on one's group membership (e.g., sex, race, and religion) and not on one's individual characteristics [5, ch. 1]. In order to understand how infertility affects women as a group in the global South, we need to rely on an approach, like feminism, that is grounded in oppression theory.

## The Deleterious Effects of Infertility for Women in the Global South

There is much debate over whether infertility is a disease and thus necessitates medical treatment. Some who argue that treatment for infertility is elective – not medically necessary – would probably claim that it should be excluded from the discussion of health-care priorities and allocation. We do not wish to engage in this debate; rather, we will take it as a given that infertility is a disease and approach the topics of ART in the global South from a different angle. Relying on the World Health Organization's broad definition of health – "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" – we claim that infertility engenders a state of non-health for women in the global South [6]. As we show with examples from various geographic areas in the global South, infertility often leads to a variety of deleterious social, economic, and health effects for women.

Before moving on, however, it is important to note that regardless of which partner (the woman, man, or both) is the cause of infertility, it is generally the woman who is blamed and hence suffers the consequences of infertility.

### *Africa*

In many African countries, the purpose of marriage is to produce children. Children are economically necessary to married couples because they carry a part of the workload and are responsible for taking care of their parents when they become elderly and unable to care for themselves. People without children have less help with work tasks, thereby causing women (and men) to take on more work themselves. Women are made especially vulnerable in old age if they are childless because they are sometimes seen as a disposable segment of the family and population.

There are also religious reasons why children are so highly valued in many African cultures. For example, in certain cultures, children are thought to play an active role in their parents' transition to the afterlife. As Godfrey Tangwa explains, "on the approach of death, a childless person is particularly terrified because, while death is considered a transition into the realm of the ancestors, the living-dead, life, well-being, and prosperity in that realm is believed to depend on the reciprocal interaction between the progeny and the ancestors, between the living kin and the living dead" [7, p. 56]. In other words, women and men without children may be quite stressed and fearful at the end of life because they do not have children to assist them in a good afterlife.

## *Asia*

Women in China, India, and other countries in Asia typically have a low social status. One of their key roles – if not the key role – is to produce healthy offspring, namely sons. Having sons increases a woman's social status. Women who do not have sons, or worse yet, do not have any children, have a lowered social status. Indeed, women suffering from infertility have a dramatically diminished quality of life. They experience social ostracism ranging from the aforementioned lowered social status to divorce [8, p. 78]. Moreover, they typically experience psychological, emotional, and physical abuse not only from their husbands but also from their families and community at large. It is estimated that nearly 70% of infertile women are punished in a violently physical manner for their infertile condition because it is seen as a failure by spouses and family members [9, p. 17]. In addition to this abuse, infertile women "have nobody to talk to or share their pain with. The childless woman is considered inauspicious and feels unworthy and unwanted" [10, p. 67].

## *Middle East*

As in Asia, in developing parts of the Middle East, women rely upon their procreative abilities to establish their social status. According to Gamal Serour, "Prevention of infertility and its relief are of particular significance in the Middle East area because a woman's social status, her dignity and self-esteem are closely related to her procreation potential in the family and in society as a whole" [11, p. 41]. Infertility can compromise women's sense of self, their marriage, and their role within the family. Generally women who are fertile are treated better and have a higher social status than women who are infertile.

## *Latin America*

Due to the *machismo* culture, Latin American women suffering from infertility rarely discuss their condition with others out of fear of their husbands' response.

Indeed, women feel forced to hide their infertility so they do not bring shame upon their husbands and families. Carrying the burden of their infertility without any social support can be stressful and socially isolating.

In addition to suffering in silence, Latin American women who are infertile have limited treatment due to the strong influence of Catholicism and Christian Evangelicalism on their countries' official policies regarding ART. For example, an amendment to Costa Rica's Constitution only allows homologous insemination and bans all other forms of ART. In Mexico and Argentina, a woman may only receive ART if she is married or in a relationship. While, there are many countries in Latin America that lack any policy agreement on ART. The religious conservatives usually shape informal policy so that it lines up with specific religious beliefs. Infertile women often have to flee their country to receive treatment at an exorbitant cost that most cannot afford [3, pp. 32–34]. These ART policies and practices perpetuate an oppressive environment in Latin America by denying women reproductive autonomy.

## *Global South Overall*

The brief descriptions we have provided on various geographic regions in the global South illustrate the severe and interrelated social, economic, and health-related consequences of infertility. Infertility adversely affects women socially by leading to lower social status and ostracism. The way women are treated by their husbands, families, and communities (e.g., how much food they eat, whether they suffer physical abuse, and whether other community members trade with them and help them) heavily depends on their social status. At the extreme, infertility can lead to social death: being expelled from the community. In countries where women are not permitted to have jobs outside the home and/or are financially dependent upon men, expulsion from the community, or even just divorce, can be socially and economically devastating.

Infertility can also negatively affect women's economic stability in other ways. For many families in the global South, the ability to reproduce is necessary for economic survival, particularly later in life. From early ages, children contribute to the family's workload and even work in the public realm to help make ends meet. Furthermore, children are often the means by which the elderly acquire basic necessities: "Without children, men and women may starve to death, especially in old age" [9, p. 16].

Some of the economic consequences of infertility, like lack of food, can lead to health-related problems, such as malnutrition. But there are health-related problems due to infertility that are independent of economic problems. For example, infertile women are more likely to be the victims of physical and emotional abuse. Also, infertile women may be denied basic necessities or forced to do extra labor. In sum, women who are infertile face serious social, economic, and health-related consequences.

## The Big Objection: There Are More Important Priorities than Infertility

Although many may agree that infertility significantly burdens women in the global South, they are still not convinced that ART should be a high priority. The main and most common objection to the reprioritization of ART boils down to a fundamental disagreement about health-care resource allocation. Some argue that in a low resource setting, money and resources should go to the most basic of needs. In the health-care realm, this means money should be funneled into established treatments on the primary care level which, for a given sum of money, benefit many people, e.g. vaccinations and malaria nets, rather than less established or investigational procedures which, for the same sum of money, only help a small minority and are often thought to be "elective." The foundation of this utilitarian argument is that money and resources should go to the most pressing health-care problems, to conditions that affect a large demographic, and to procedures that are cost effective and have a high success rates. Since ART do not meet any of these criteria, then according to this argument, it should stay at the bottom of the prioritization list [9, p. 15].

## Three Responses to the Objection

### *Response 1: ART Need Not Be Expensive*

It is common knowledge that ART are expensive, but we need to question why they are so expensive in order to determine if cheaper and more accessible ART are possible. One reason many cannot afford and/or do not have access to ART has nothing to do with ART themselves, but rather with the laws and policies (or lack thereof) surrounding them. There is no legal regulation of ART in the United States, which has allowed doctors to set the price of ART as they see fit. Given that there are wealthy infertile individuals willing to pay exorbitant sums to have biological children, the cost of ART has risen to what these individuals are willing to pay, which is much higher than the actual cost of services. The result is many infertile individuals in the US who cannot afford ART. Just like the lack of ART regulation can, perhaps inadvertently, deny access to some infertile individuals, so too can severe legal restrictions for ART. Although numerous restrictions on ART make it difficult for all individuals to afford and access ART, the poor and uneducated are especially hard hit because they usually do not have the resources or the knowledge to circumvent the system or to opt for medical tourism.

Mitigating legal barriers will not make ART more affordable and accessible because ART, as they are currently practiced, are expensive. Yet, ART need not be expensive. According to fertility specialists like Willem Ombelet and Alan Trounson, the delivery of ART can be tweaked so that they are more affordable to those in the global South. Part of the reason ART are so expensive, they claim, is that they are tailored to those in the global North where high-technology tools are readily available. Ombelet and Trounson believe that "Western laboratories are replete with technology that costs tens of thousands of dollars, but much of it can be done away with" [12, p. 977]. Much of the high-technology tools and expensive drugs can be replaced with low-cost alternatives that are just as or almost as safe and effective. For example, in the global North, most women use 30 vials of gonadotropin per treatment cycle, which produces up to 12 eggs, at a cost of $300–$450. Gonadotropin could be replaced with clomiphene citrate, which produces fewer eggs (approximately four), but 15 pills only cost $1 [12, 13, p. 977]. Using lost-cost alternatives can reduce IVF from around $10,000 in the global North to just $300 [14].

Even with these astonishingly reduced prices, many individuals in the global South still struggle to afford ART. Some have argued that the international community should take a more active role in reconciling the high cost of ART worldwide. Global health experts Abdallah Daar and Zara Merali, for instance, suggest a partnership of public and private enterprises formed specifically for the development of ART in developing countries [9]. One such organization, the Low Cost IVF Foundation, was established in 2007 under the auspices of the Swiss Ministry of Internal Affairs. Here is the organization's mission statement[2]:

> The Low Cost IVF Foundation is promoting the provision of simplified clinical IVF services for a minimal cost that will allow couples, who could otherwise not afford it, access to IVF treatment for their infertility. The Foundation aims to demonstrate that the material costs for a cycle of IVF can be less than 200 € [just under $300 in today's currency conversion]. The costs will vary from country to country, but the Foundation's objective is to minimize costs to make treatment affordable to a much greater number of people [15].

With centers in Tanzania and South Africa and a third center that opened in Sudan in October 2009, the Low Cost IVF Foundation is proving that it is possible to provide ART at a low price [14]. Given the successful work of the Low Cost IVF Foundation, the argument can no longer be made that ART are far too expensive to be considered in health-care allocation in the global South.

## *Response 2: Justice and the Right to Reproduce*

As previously mentioned, part of the reason that ART are typically considered a low priority is that they are seen as elective procedures, not medically necessary ones. Even people who think infertility is a disease often do not prioritize ART because

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[2] Given our arguments in the previous sections, it is worth highlighting this part of the extended mission statement: "The Foundation seeks to identify donors that will provide funds to establish Low Cost IVF Clinics in low resource economies where having a child greatly improves the social status of a woman and reduces her risk of being rejected from her family and community and left destitute." The members of the Low Cost IVF Foundation recognize the degree to which infertility can harm women in the global South and thus part of their reason for creating this foundation is to help these women.

infertility is not life threatening. Nonetheless, other diseases that are not life threatening are prioritized, particularly by the international community. For example, a cleft palate is not a terminal condition, but it is a physical deformity that can make individuals' lives significantly more difficult. Individuals with a cleft palate not only experience health problems but also typically face social and economic challenges, such as ostracism. Nonprofit organizations, notably Operation Smile, have emerged to provide care, especially corrective surgery, for those with cleft palate in the global South.

While there are many large scale nonprofit organizations addressing reproductive health, most of them do not include assisting infertile individuals in the global South [16, pp. 615–616] (the Low Cost IVF Foundation is a notable exception). Rather, they mainly provide contraception and maternal care (including childbirth). There is no doubt that these are extremely important foci, but reproductive autonomy is not satisfied by the right to contraception and maternal care. There is also the right to have children. Yet infertile individuals in the global South, as well as poor individuals in the global North, are rarely able to afford ART that would enable them to have biological children. It is unjust, and perhaps reflects a tacit eugenic view about the poor's worthiness to reproduction, that the ability to have biological children is often based on one's socioeconomic status [17, p. 179]. The lack of access to ART in the global South combined with many reproductive health organizations' implicit and often explicit goal of population control in the global South can be seen as promoting a racist agenda [18].

Dorothy Roberts eloquently argues for a broader understanding of reproductive autonomy that promotes social justice:

> "Reproductive liberty must encompass more than the protection of an individual woman's choice to end her pregnancy. It must encompass the full range of procreative activities, including the ability to bear a child, and it must acknowledge that we make reproductive decisions within a social context, including the inequalities of wealth and power. Reproductive freedom is a matter of social justice, not individual choice" [19, p. 6].

Thus, in order for women in the global South to have full reproductive autonomy, they must be able to control the number of biological children they have, which means both preventing unwanted pregnancies and enabling wanted pregnancies.

## *Response 3: Women's Development, Countries' Development*

The broader understanding of reproductive autonomy as a matter of social justice discussed in the previous response would have positive outcomes not only for individual women and women as a group but also for developing countries. Specifically, this understanding of reproductive autonomy would encourage and enable "development," especially economic development in the global South. Part of what hinders development is the oppression of women, namely gender discrimination and women's low social status. Nicholas Kristoff and Sheryl WuDunn argue that "in many poor countries, the greatest unexploited resource isn't oil fields or veins of gold; it is women and girls who aren't educated and never become a major presence in the formal economy." They furthermore claim that aid directed toward micro-finance loans, education, and health care tends to be more successful economically [20].

The reason for this is that when women receive better opportunities, education, and health care, they become more autonomous and empowered. Women's education and employment are crucial for equal gender relationships. Education and work outside the home are significant sources of empowerment for women. It is well documented that female literacy is a necessary component for improving the lives of women and their families in "developing" countries. Specifically, education is "an essential factor in preparing people to lead healthy, socially rewarding, and economically productive lives" [21, p. 103]. Education and employment empower women, providing them with the knowledge and confidence to make their own reproductive decisions or to make joint decisions with their boyfriends/husbands. Making joint decisions is typically easier for educated women because men with educated partners are usually less likely to exhibit male dominance in the reproductive realm [22, p. 223]. When women are educated and when they work outside the home, there is a greater probability that men will perceive them as equals, rather than as subordinates. Consequently, men will be more willing to affirm their reproductive autonomy and to support their decisions.

Women's increased autonomy facilitates their participation in the economic realm, which benefits the entire country. Women's education and employment are good for the economy, as it means not only more workers contributing to the formal economy but also more skilled workers. Promoting women's reproductive autonomy also aids countries' economic development by creating new jobs in reproductive health. An expansion of women's reproductive rights coupled with a cost reduction for ART could lead to a demand for ART centers in developing countries, as empowered women are more likely to seek treatment for infertility. A decrease in price would make ART a more feasible option for individuals in the global South, especially those who do not have the financial resources to seek ART abroad. Wealthy individuals in the global South who currently rely on international medical tourism may choose domestic ART centers instead due to convenience and cost. If an increased demand for domestic ART centers arises and leads to the establishment of such centers, it would help the local economy by providing jobs.

## Infertility and Cancer

We have spent the majority of the chapter explicating the severity of infertility for women in the global South and arguing that treatment of infertility via ART should be made a higher priority. We now return to the topic with which we began, cancer. Women with cancer, just like women with infertility, typically suffer from more than just their disease. Having cancer engenders various adverse social, economic, and health-related effects for women. These negative consequences are usually due to cultural reasons, specifically patriarchal norms. The stigma associated with cancer can bring shame upon a woman and her family, which may cause spousal violence and social ostracism. Stigma, along with other sexist factors like “discrimination, machismo, and a tendency to reduce women to body parts,” can also lead to a delay in cancer screening and treatment. Screening and treatment can also be delayed because, in some extremely patriarchal societies, a woman needs her husband’s permission to see a doctor and may even need him to accompany her. These delays can prove deadly. For example, over half of all breast cancer cases in Mexico are detected in stage 3 or 4, when it is significantly more difficult to treat. By contrast, approximately 60% of breast cancer cases in the United States are discovered at stage 1; only 5–10% of cases in Mexico are detected at this stage. The symptoms of cancer and the side effects of cancer treatment (especially later stage cancer treatment) can interfere with, and even prevent women from, fulfilling their gendered responsibilities of bearing and caring for children, sexually satisfying their husband, and sometimes working to support the family. Given that maintaining these responsibilities is oftentimes the only way women can gain status, not being able to meet these responsibilities can have deleterious effects on women [23]. In sum, the social, economic, and health-related consequences of cancer for women in the global South can be quite similar to and just as severe as those due to infertility.

The possibility of infertility for female cancer patients in the global South makes these already disadvantaged women even more vulnerable. Indeed, these women are doubly burdened: they suffer from a serious disease and the treatment for this disease may render them infertile. On top of that, they typically experience adverse social, economic, and health-related consequences as a result of both cancer and possible infertility. Even if they retain their fertility following cancer treatment, the risk of infertility may have already caused irreparable damage (e.g., a reputation of being infertile and thus unmarriageable).

Significant cultural change, especially regarding gender roles, is needed to prevent the adverse consequences women face due to both cancer and infertility. However, such a cultural transformation can take a very long time and will require a complete shift in ideologies, for which the possibility of success is uncertain. A quicker and more concrete way to alleviate some of the adverse consequences for female cancer patients is to provide affordable and easily accessible fertility preservation technologies. While the option of fertility preservation technologies would not minimize (at least not directly) the negative cultural effects of cancer, these technologies would grant women the opportunity to have biological children post-treatment, thereby mitigating or averting the social burden women experience because of infertility.

Fertility preservation technologies do not guarantee healthy, live births, and some women will still suffer the stigma of infertility.[3] Overall, these technologies could help many women by decreasing the possibility of adverse consequences due to infertility. Furthermore, motherhood is important in many cultures; ART would offer

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[3] It is beyond the scope of this chapter to discuss the stigmas associated with using ART.

women with cancer in the global South who desire biological children this possibility. Providing fertility preservation technologies before cancer treatment is a good short-term and long-term solution for decreasing the harms that women generally experience due to infertility and cancer.

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# Chapter 19
# Oncofertility and Informed Consent: Addressing Beliefs, Values, and Future Decision Making

**Felicia Cohn**

## Introduction

Imagine every parent's nightmare… your sweet, vibrant daughter has just been diagnosed with cancer. The doctor is talking to you, but all you hear is "cancer" and all you can think about is the possibility that she may die. Now that the diagnosis is made, the doctor is anxious to begin treatment. He is describing the treatment, its benefits and burdens, and the schedule. Suddenly, though the "c-word" continues to buzz in your ears, you hear the side effects of treatment – hair loss, nausea, fatigue, weight loss, and infertility. "Infertility?! My baby may never be able to have babies?!" You have not yet processed the diagnosis, or come to terms with your child's mortality, and now this. Before you have even consented to the cancer treatment, the doctor is asking if you would like to enroll your daughter in an oncofertility research protocol. It means delaying treatment and further taxing her (and you) physically and emotionally. Time is of the essence, since the cancer treatment must begin as soon as possible. Not one decision but two, and both seem impossible.

The informed consent process is the backbone of physician–patient communication, and although fundamental to the practice of medicine, this process is completely inadequate in so many ways. Since the Supreme Court ruled that "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" in the 1914 Scholendorff case, informed consent has been a legal standard for assuring that patients are informed, understand the information provided, and are afforded the opportunity to make autonomous decisions [1].

As a conversation between people, the informed consent process is imperfect. A good process involves disclosing information about the patient's condition, need for treatment, treatment options, risks, and benefits of those options; assuring that the patient understands that information; and allowing the patient or family member as the patient's surrogate to make a voluntary decision. Numerous questions

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plague the process: How much information must a physician disclose? How great must a risk be to necessitate disclosure? How can patient understanding be assured? Such questions reflect the formal process as it has evolved legally and ethically, but do not begin to get at broader issues. Clinical oncofertility trials provide an interesting context for considering the adequacy of the informed consent process. Is informed consent truly possible when making "a high-stake, time-sensitive, emotionally charged, nested decision"? [2]. Difficulties for patient/family decision making lie in at least three areas:

(1) ability of the patient/family to understand the nature of treatment and research;
(2) ability to distinguish the treatment and research, particularly in assessing risks/benefits each; and
(3) ability to account for both the immediate and long-term implications of the decisions made.

Each of these demonstrates the frailty of the informed consent process and the tenuous nature of some of the decisions patients or their families make. Much has been written about the first two issues particularly in relation to the limits of informed consent following serious diagnosis in the research context. For example, informed consent requires that patients have adequate knowledge to make informed decisions. This means that the information be disclosed and understood. Yet, studies indicate that patients may not have the necessary knowledge or may not understand what they have been told [3, 4]. Further, studies suggest that a "therapeutic misconception," in which a potential research subject conflates the separate goals of treatment and research, may complicate informed consent for research trial enrollment [5, 6, 7].

My focus will be on the third issue, one that is particularly poignant in the context of oncofertility research and will require longitudinal study as (and if) oncofertility treatments move from the domain of research into standard practice. Such consideration is essential for adequate informed consent, as a decision to enroll in a study now will impact decisions made over the patient's lifetime. Understanding the implications of the decision requires an examination of the conditions under which the decision is made. Among these conditions are beliefs about the goals of the research (i.e., individual fertility preservation) and the emotional stake the patient and her family may have in the decision. Once made, the decision will likely require future decision making. I will briefly consider each issue in an effort to frame its significance for informed consent.

## The Belief that Fertility Is Preserved: Immediate Risk for Future Benefit

The newly diagnosed cancer patient learns that her treatment may leave her infertile. Good statistics on the likelihood of this, if they are available, may still be unclear as they apply to populations and not individuals. The oncofertility trial appears to be the young patient's best, and perhaps only hope, of assuring future fertility. To make a decision, the patient/family must assess their beliefs about fertility and understanding of the research. At least four related considerations seem important in this scenario.

First, is the physician willing to offer a fertility preservation procedure such as ovarian tissue cryopreservation? With many cancers, immediate treatment is desirable, if not necessary, to avoid additional risks from the cancer itself. A physician may believe that the potential to save the patient's life takes precedence over all other considerations. In the physician's risk/benefit analysis, potential or even likely infertility may simply be a price paid for preserving life. This is separate from the patient's/family's own calculus but may profoundly affect whether the patient is even offered fertility preservation options. Some physicians act as technicians, merely offering and objectively explaining all treatment options available so that the patient/family is solely responsible for decision making. Others more paternalistically direct treatment, while still others seek to counsel and negotiate with patients. The course of the conversation results from the physician's beliefs and type of physician he/she is [8].

The physician's concerns about impact of the research on treatment may be compounded by a second concern: Is the procedure likely to result in fertility preservation? Both physician and patient must assess the trade-off between the delay of cancer treatment and potential for fertility preservation. Ovarian tissue cryopreservation does not guarantee that the patient will be able to have her own babies in the future. Even if the research demonstrates success, similar success for a particular patient is not assured. Efforts to preserve fertility have no therapeutic value for the treatment of cancer, may interfere with the initiation of cancer treatment, have independent risks, may result in unacceptable side effects, and ultimately may not pay off. One study found that research participants did not understand that clinical trial treatment is not standard treatment and may involve additional risk [9]. For some, the risks beyond the impact that participation in the study will have on the cancer treatment may not be acceptable. For example, beyond the usual risks associated with a surgical procedure, removal of an ovary or part of an ovary may result in early menopause and its attendant risks for the patient. This might be weighed against the potential risk of infertility and the potential for success of the developing oncofertility technologies. Consideration of these risks is necessary though may be difficult to separate from the larger context of the risks and benefits embedded in the cancer treatment. Others argue that clinical research trials are consistent with therapy and may be good therapy themselves [10]. While this argument pertains to clinical trials for the primary diagnosis, in this case a clinical trial for an experimental cancer treatment, it more broadly suggests an independent value for clinical trials. A patient worried about her future fertility may fare better in her cancer treatment if this concern is addressed.

Addressing a patient's concerns about future fertility, however, may entail actually thinking about the future, not just the more imminent possibility of infertility. With most cancers, the primary concern is preserving life and restoring the patient to a cancer-free existence. The infertility issue may be a significant distraction, which may be either positive or negative. For some, the opportunity to deal with a different problem may be welcome relief from dwelling on the cancer diagnosis. For others, however, it may mask important issues that the patient/family must understand in making any treatment or research decision. Considerations of fertility are inherently matters for long-term thinking, particularly in the case of a child or adolescent patient. Decisions about bearing children will usually not be made for years or even decades. Pursuing fertility preservation could become important symbolically; it represents a normal, healthy future in which starting a family is possible. Whether this representation is realistic or optimistic is necessarily part of a good informed consent process. From a research perspective, the patient's enrollment in a research protocol may be of great benefit whether the patient lives or dies or goes on to make use of the opportunity for bearing children or not. But for the patient, participation in the protocol may only be valuable, setting aside general arguments about the importance of altruistic behavior, if there will be a real opportunity to benefit from it in the future. Considerations of the symbolic value of the procedure, i.e., "what does it mean to the patient?" are likely to impact the decision to participate.

Finally, risks, benefits, and symbolism aside, the decision-making process cannot avoid addressing the fundamental question: Does the patient want babies? While some girls declare their desire for a baby from the moment they pick up their first doll, most will not have seriously considered this even in the abstract. Thus, the entire decision about participation hinges on anticipating future desires. Even those girls who claim to have no desire for children may want to maintain the option, recognizing that they may change their minds. If the families are involved in this decision-making process (and they likely are given that the patient is a minor), it may be difficult to separate a parent's desire for future grandchildren from the patient's wishes. This may lead to conflict if the patient prefers to focus on the present treatment of her disease while the parents insist that she consider her future or vice versa. While the parents retain decision-making authority, such weighty decisions about life and death and procreation suggest the need to include the minor in the process, as developmentally appropriate. Indeed, the American Academy of Pediatrics recognizes the important role of the minor in medical treatment decision making and calls for patient assent for treatment [11]. Consent and assent require concrete decisions about abstract situations and beliefs that may not yet be clear.

## Emotional Implications of the Decision-Making Process

Among the risks and benefits that might be discussed as part of the informed consent process are the emotional implications of the decisions to be made. At least two warrant consideration: the very role of emotions in this decision-making process and the relationship this decision has to the child's sexuality.

Any decision about infertility will likely be as subject to emotions as to rational considerations, even without the greater context of cancer treatment. The decision can be dressed in the language of logic, with a recitation of benefits and risks and an accounting of personal values. But, fundamentally, the decision to have a child is among the most emotion-laden decisions one can make and any decision that relates to childbearing seems likely to be as emotional. That does not mean that there are not good and bad reasons, pros and cons, arguments from responsibility and obligation, considerations of context, and other elements of objective argumentation, but ultimately, it comes down to whether one wants a child or not. Desires often exist independent of good judgment. To further complicate matters, in this case the decision is probably not yet about whether the patient wants a child, but about what the child is likely to want in the future. Emotional decisions may not reflect an individual's core values or may not be reflective at all. It seems logical, in the face of immediate jeopardy to one's fertility, to reach for an insurance policy, to take action that might preserve the option of having children in the future. But it may be just as logical to refuse enrollment in an oncofertility trial out of a reasonable preference to commence with the cancer treatment as soon as possible, to worry about living first and having babies later. Which is more logical? In the end it may not matter as the emotional reaction – panic, desire, fear of infertility, or dying – may be the true arbiter of decision making. Emotional response is certainly human and can be very valuable, but may not suggest the decision one would otherwise make in less difficult and urgent circumstances. As Jodi Halpern notes,

> . . . while emotions might help us notice what is morally or humanly relevant, they are not always reliable indicators of our deep and long-standing values. Consider how romantic passion or fear of loss compel our actions and even give us a sense of certainty – and yet both can also feel quiet alienating in retrospect. The strength of an emotional feeling does not necessarily reveal how integral the emotional view is to our internal beliefs and values [12].

When a weighty decision must be made quickly, with little time or energy for rational analysis, emotion may become the primary guide. It may not lead one astray, but can explain emotional anguish later on. Acknowledging this possibility, if not accounting for it, seems a necessary part of the informed consent process.

In addition to the emotions triggered by the possibility of infertility are those due to the discussion itself. Any discussions related to fertility may be difficult or at least uncomfortable. Parent and child are forced by circumstances to discuss the child's fertility, a topic inextricably linked to sexuality. After just facing a child's mortality, they now must also consider the child as a sexual being. Usually, the preference is for adults to make decisions about childbearing for themselves when the time comes. However, when cancer treatment in a young or adolescent girl poses the risk of infertility, suddenly she is forced to consider very adult topics, without the benefit of whatever preparation the status of adulthood confers or from the context of a committed relationship in which family planning ideally occurs. Parents are also put in the position of making decisions that only indirectly bear on them. While some parents may be overbearing in their pursuit of grandchildren, they usually do not have to make decisions that will affect whether biologically related grandchildren are even a possibility. Through this emotion-laden lens, it seems impossible that the family, and the child herself, will ever see this young patient in the same way again. A child involved in the decision-making process may come to view herself as more adult, more capable of making decisions, including those about sex, or may be troubled by her inability to deal with such weighty issues. Parents may also view the child differently, perhaps more mature or more vulnerable.

Debates about sex education and the human papilloma virus (HPV) vaccine may be instructive. The HPV vaccine was developed to prevent the spread of the virus linked to cervical cancer and is ideally targeted to 8- to 10-year-old girls who are less likely to be engaged in the sexual activity that could expose them to HPV. Parental response to the vaccine has been mixed. Parents are divided on when sex education should begin and the responsibility of the parents in providing the education. When the HPV vaccine was introduced, parents were concerned that it would prompt earlier discussions about sexuality than they were prepared for and could serve to encourage their young daughters to have sex. Studies on the implications of the HPV vaccine suggest that families may not be ready. One study, for example, found that some parents preferred to delay immunization and the sex education they believed should accompany it, at least until secondary school. The investigators note, "Some parents were unable to acknowledge that their children could be regarded as sexual and therefore there was no need for a vaccine to protect against [a sexually transmitted disease]" [13]. Other parents preferred that the vaccine be offered to younger children or babies to limit the child's curiosity and circumvent the need for discussion about sexuality. Similarly, the unavoidable link between fertility and sexuality may intensify emotions and cloud judgment about both cancer treatment and fertility preservation choices. In addition to discussing treatments, research, and the benefits and burdens of each, the family may need help sorting out their emotional responses.

## Future Decisions

Electing to preserve fertility feels like a final decision. Decision made, the patient undergoes a procedure to attempt to preserve her fertility, removing all or part of an ovary, banking eggs, or creating and banking embryos. Once done, she can proceed with her cancer treatment. If the cancer treatment is successful and the patient survives, however, the story is only just beginning. At some point, whether it turns out that she is infertile or not, she must decide what to do with that stored material. For a young girl, it may be decades before she wants or needs the materials. In the meantime, she and/or her parents must make decisions about storage and ultimately, she or someone else must decide what to do with the materials.

Fertility preservation procedures may include storage for some limited time, at least while a research protocol is active, but eventually the former patient/family must make decisions about ongoing storage. Storage fees may amount to thousands of dollars before she is ready to use the materials. This may feel like money well spent for someone rendered infertile by their cancer treatment who desires a baby or a waste for someone whose fertility persists despite treatment or decides she does not want children; such is the nature of any "insurance policy." The storage issue may seem easy, but can force the former patient to revisit her illness experience and question her desires, on an annual basis. Interviews of women who stored embryos after in vitro fertilization (IVF) illustrate the potential emotional burden. One woman was asked about surplus embryos at the beginning of the IVF process, but says she was unable to consider embryos she might not want or need when her focus at the time was on having children she so desired. When the first bill for the extra embryos arrived after she had children, she said, "I was petrified… There was no practical reason to keep them. I just wasn't ready to make the decision not to keep them." Each year she pays $600 for her inability to decide what to do [14].

Even if the fee is not a factor, long-term storage raises other questions. A young girl may not be ready or interested in having children for 10, 20, or even 30 years. Will the tissue still be viable? The experience with frozen ovarian tissue is too recent to know, but frozen sperm has proven viable for up to 21 years [15]. How will freezing and thawing affect the tissue? Will using the tissue be safe after extended periods of storage? What if the storage facility goes out of business, suffers a power outage, etc.? Once the patient is ready, will she have the means to make use of the materials? None of the questions have answers at this time, but will require consideration at some point. The concern now is whether these questions merit consideration before enrolling in a fertility preservation protocol.

Beyond the question of storage and maintenance are questions about disposition of the materials. The research protocol may address the issue at the time of enrollment. In the event that the patient dies, the patient/family may be asked to select either donation for research purposes or destruction of the remaining tissue that was collected for research. Whatever box was checked may no longer reflect the family's preferences after the death of the patient or the patient's expressed wishes before her death. These preferences may include options not offered at the outset of the trial. Further, the tissue designated for the patient's own use is sent to a third-party storage facility and is never under the purview of the researchers, though it may be subject to particular requirements of the storage facility or fertility center. Can a living patient or a family direct that the materials be used in other ways, for example, donated to the patient's sister or even to a stranger, for procreative purposes?The history of IVF is full of tales of individuals fighting over what is to become of frozen embryos. The IVF experience also demonstrates that a number of frozen embryos exist in limbo, abandoned, and unfunded by their creators. The Ethics Committee of the American Society for Reproductive Medicine considers embryos abandoned after 5 years of unpaid bills and futile efforts to contact those responsible for the embryos [16]. According to this standard, the facility may then thaw and discard the embryos. Yet, the storage facilities appear to have been largely paralyzed to act on the policy [17]. One study indicates that most clinics (95%, 166 clinics) attempt to contact the people who have stored embryos regarding disposal, even if the consent to future disposal had already been provided in writing. Most of those (66%, 110 clinics) did not proceed with disposal if those who created the embryos could not be reached [18]. The researchers describe a sense of reverence for these embryos, which persists even in disposal processes that may resemble religious ceremonies. While the same moral weight may not attach to ovarian tissue, comparable emotional import might, occasioning similar controversies and familial distress. Or, it may be that the disposal of preserved ovarian tissue is more like the disposal of frozen sperm or even the disposal of other unwanted tissue removed during surgical procedures. The reaction will likely vary with the context of the disposal and the personality of the family. Regardless, a full informed consent process may have to acknowledge the need for future decisions about storage and disposal.

## Conclusion

No informed consent can cover everything, but legally and ethically, physicians and researchers are obligated to disclose information relevant to decision making, assure the patient/family understanding, and support the process of making a voluntary decision. Decisions about undergoing fertility preservation procedures highlight some of the shortcomings of the informed consent process and raise questions about the very possibility of an adequate informed consent. Generally the process focuses on the immediate treatment and/or research options, but for some decisions this may not be enough. Decisions about oncofertility research and treatment require attention to personal values, emotions, and implications for long-term decision making, and these discussions take time. In studies of clinical research decision making for minor patients, parents consistently cite the need for more time to make the trial decision [19–25]. "[P]hysicians should plan the consent process in such a way as to allow for as much time for decision-making as possible within the limits of the child's medical condition and the particular trial protocol being offered" [26]. Unfortunately, this important discussion often must occur quickly, perhaps over only hours or days. Is it possible to address or even raise these issues under the pressure of time and serious diagnosis? This is more than just a rhetorical question. For informed consent to avoid being relegated to mere legal requirement, this process of communication must be recognized as a fundamental driver of the physician–patient relationship and quality health care. Short time frames and urgent decisions are no excuse for insufficient efforts to convey the magnitude and implications of the decisions to be made. The patient and her parents, overwhelmed by their situation and the decisions they must make, need help navigating the issues they must consider. It is the physician who is best situated to help them make these decisions. The impossible can only come to seem possible with the best communication under the circumstances. This means at least disclosing answers to questions the patient/family will likely not know to ask and helping them understand what they are doing, well before seeking signatures on an informed consent form.

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# Part IV
# Religious Perspectives

# Chapter 20
# Bioethics and Oncofertility: Arguments and Insights from Religious Traditions

**Laurie Zoloth and Alyssa A. Henning**

## Introduction

This chapter seeks to explain our preliminary reflections on how different religious communities might use their texts and traditions to respond to and assess the ethics of oncofertility research and technologies. Specifically, this chapter will briefly explore the Catholic, Evangelical Christian, Muslim, Jewish, Hindu, and Buddhist traditions and their anticipated or potential contributions to the ethical discourse surrounding oncofertility. The chapter will sketch a few characteristic principles and describe some preliminary responses from practitioners that may guide each religion's traditional stances toward reproductive technologies and procreation. The material presented herein builds upon exploratory research by two classes of undergraduate students at Northwestern University. The author's additional research sought out additional sources and considered additional religious traditions. The students' research included interviews with local ministers, rabbis, faith communities, including campus ministers, and also student participants in various religious traditions. The clergy, intrigued by the questions raised by the research, suggested some of the preliminary sources and general directions pursued in this chapter.

Scholars speculate about the anticipated acceptance of or difficulty with particular aspects of oncofertility technologies in each tradition. Many traditions employ case-based reasoning to address ethical questions. Because oncofertility science is still largely theoretical, as yet affecting only a handful of first cases, most religious communities have not yet deliberated upon the ethics of oncofertility. We anticipate far more responses will result should the technology, if successful, become widely desired or available. We wish to add a final caveat: because religious communities exist in cultural and historical contexts, in general, while principles and stances derived from religious sources often emerge from formal documents, these may not represent the fullness of the actual practices of many individuals who identify with a particular religion. Additionally, each of the traditions we sampled is part of a much larger religious tradition containing multiple denominational, congregational,

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and geographic subgroups with varied relationships to the more general positions outlined in this chapter. The core of the chapter outlines suggestions for considering possible contributions of each religious perspective to broader ethical discussions about oncofertility. Any scientific enterprise, but especially one concerned with the creation of families, will benefit from the broadest consideration of the arguments made by multiple traditions and viewpoints, particularly when these varied insights are brought into dialogue with one another. We contend that bioethics is a reflective and reflexive conversation and operates best when the discourse is enriched by arguments that extend beyond the considerations of the market or the curiosity of research scientists.

## Why Religion?

Since the early 1990s, American scientists have been asked to incorporate ELSI (Ethical, Legal, and Social Implications) research into their projects. Ethical and social implications are deeply intertwined with religious traditions and communities. Religious perspectives and the arguments derived from religious texts and communities may contribute to public and scholarly bioethics discourse in a variety of ways – both practical and theoretical – depending upon the discussion's goals. Physicians and clinical researchers, who will encounter families with a diverse set of norms and customs, will benefit practically from basic knowledge of and familiarity with religious perspectives in at least two ways. First, familiarity with even the most rudimentary religious beliefs may help clinicians better understand and negotiate the dynamics of each physician–patient relationship. At the clinical level, medicine requires beneficence. But this requires a shared sense of "the good," a task that is impossible without a frank discussion of essential notions of morality. Understanding a patient's religious commitments is one critical part of this task, so that physicians and family members may better communicate with a patient who draws upon religion to cope with an illness or make decisions about medical care. Patients may consult, invoke, or defer to religious beliefs, sources, or leaders when making decisions about their own medical treatment or treatment for a surrogate (e.g., a child or incompetent parent or partner), including decisions about whether to seek access to oncofertility research protocols or technologies and determining which types of research protocols or technologies they wish to pursue.

Second, knowledge about religious perspectives may prove relevant when shaping a research agenda. Researchers may be influenced by their own religious, ethical, and moral backgrounds when thinking about the types of illnesses they will study and the methods by which they are willing to study them. For example, researchers may turn to their religions for guidance when deciding whether or not to use embryos or fetal tissue as research materials. Additionally, knowledge that a particular religious community lacks an ethically acceptable treatment for an illness may motivate researchers to focus on developing alternative treatments that could be utilized by patients in that particular community. For instance, researchers may be moved to develop an artificial blood replacement that might be acceptable to Jehovah's Witnesses who would otherwise refuse blood transfusions. Finally, information about religious perspectives may guide researchers to design studies that are less likely to cause controversy in public policy; for example, by developing novel fertility preservation technologies that will appeal to a broader cross section of the public by avoiding embryo freezing.

Religious perspectives also facilitate theoretical conceptualizations of the ethical questions that ought to be considered as researchers, physicians, and patients move forward in the field of oncofertility. By fusing cancer treatment and fertility, oncofertility challenges us to ask questions about our conceptions of, and the meanings we ascribe to, illness, healing, mortality, family, and suffering. Different religions may identify different questions raised by a new technology as the most ethically pressing. These questions may further differ from the questions that dominate secular ethical discourse. Thus, religious perspectives may direct our attention to questions we might otherwise overlook; they may also sufficiently shift a conversation's focal point to move discussion beyond a particular, ethically entrenched gridlock. For example, Benjamin Freedman argued that Judaism's duty-based ethical framework might help dislodge disputes, so common in Western, secular, rights-based ethics, over who has the right to make medical decisions for an incompetent patient. A duty-based perspective, Freedman suggested, would shift the competing parties' attention away from their personal interests in being declared the decision maker back toward the patient and what he/she is owed as a human being. Implicit in this suggestion is the claim that once the parties realize their shared concern for the patient's best interest and well-being, they may be able to stop fighting about *who* makes the decision long enough to collaborate to determine *what* decision is in the patient's best interest [1].

Religious voices may claim different types of authority in a particular discussion: for example, over the decision-making processes of members of a congregation, denomination, or entire religious tradition; citizens of a country; or all human beings. Nonetheless, religious traditions and their varied sources can enrich and inform ethical discourse, with each religious tradition contributing multiple and complex points of view. It may even be that a particular argument from a religious tradition offers the most persuasive reason for proceeding in a particular way. To visit the arguments of religion is far more than an interesting tour of exotic communities. It is to understand some of the arguments that have shaped civilizations over the last 2000 years, arguments that have been morally persuasive over strong arguments from the market or other external social pressures. It is to these varied religious perspectives that we now turn.

## Catholicism

Vatican documents convey the Catholic Church's official teachings on a variety of issues, including reproductive technologies and bioethics. Although no Vatican documents discuss the ethics of oncofertility explicitly, they provide a framework for thinking about oncofertility technologies and offer a promising resource for attempting to anticipate the ways in which the Vatican might officially assess the ethics of oncofertility in the future.

In 2008, the Vatican issued "Instruction *Dignitas Personae* on Certain Bioethical Questions." *Dignitas Personae* not only builds upon earlier Vatican documents, most notably "Instruction *Donum Vitae* on Respect for Human Life at its Origins and for the Dignity of Procreation" (1987), but also upon the Encyclical Letters *Humanae Vitae* (1968) and *Evangelium Vitae* (1995). *Dignitas Personae* acknowledged the suffering felt by infertile couples who desire children, recommending encouragement not only of adoption but also of "research and investment directed at the *prevention of sterility"* [2]. The Catholic Church may, therefore, be interested in the fertility *preservation* elements of oncofertility. *Dignitas Personae* lists three "fundamental goods" which act as guiding principles that must be respected when treating infertility: First, from the moment a sperm and an egg unite to form an embryo, that embryo is entitled to the same rights to life and physical integrity granted to all human beings. Second, partners in a marriage may only procreate with one another. Third, procreation must result from sexual union between husband and wife [2].

These guidelines place many restrictions upon procreation and the use of assisted reproductive technologies (ART), ruling out procreation by non-married heterosexual couples, all homosexual couples, and single women, as well as the use of donor sperm, donor eggs, and gestational surrogates, even by married heterosexual couples. These guidelines also prohibit in vitro fertilization or artificial insemination – even when it uses a wife's eggs and a husband's sperm. However, hormonal treatments and surgical interventions to remedy a blocked fallopian tube are permitted [2]. Catholic theologians remain divided over whether Gamete Intra-Fallopian Transfer (GIFT), a procedure by which a woman's eggs and a man's sperm are transferred to the fallopian tube, to facilitate fertilization in vivo, is morally licit; the Vatican has not issued an official teaching on this subject. According to John Haas, President of the National Catholic Bioethics Center in Boston, Catholic theologians are divided over whether GIFT replaces or assists the marital act [3]. At a minimum, special care must be taken to ensure that the husband's sperm is not collected via masturbation. Some theologians argue that if the sperm collected from the husband was emitted during sexual relations with his wife, and because the egg and sperm combine in vivo, GIFT assists the procreative aspect of the marital act. On the other hand, some theologians worry that because egg and sperm are placed in the wife's fallopian tube by a physician, GIFT entails intervention by a third party into an act that should only involve husband and wife; additionally, because not all of the husband's sperm is permitted to enter the wife's vaginal canal, GIFT may be understood as limiting the procreative aspect of the marital act, even as it aims to assist it. If a couple does choose to utilize GIFT, Vatican teachings against abortion, and the risks associated with multiple-birth pregnancies, necessitate serious consideration of how many eggs to implant for each GIFT cycle.

The first fundamental good, concerning an embryo's right to life and physical integrity, precludes embryo cryopreservation, especially since cryopreservation "presupposes their production in vitro" [2]. Research involving embryos, particularly research that destroys embryos, is also illicit. *Dignitas Personae* further cautions that oocyte cryopreservation is illicit if its intended purpose is use in artificial procreation [2]. Yet oncofertility research on oocyte cryopreservation and in vitro follicle maturation does not necessarily presume the oocytes will be used in ART that violate Vatican guidelines. Although some individuals or couples may use these eggs for IVF, Catholic couples may be able to use cryopreserved or in vitro matured eggs for GIFT. A modified version of GIFT, whereby only the eggs are transferred to the woman's fallopian tube, at which point she and her husband may try to conceive through sexual intercourse, might be facilitated by successful oocyte cryopreservation techniques and may be more acceptable to some Catholic theologians who currently oppose GIFT.[1] Oocyte cryopreservation would provide unmarried female cancer patients who abide by Vatican teachings with a fertility preservation option, enabling them to preserve their own reproductive capability so that if they get married in the future, they may procreate. Additionally, techniques in cryopreserving and then retransplanting a woman's ovarian tissue into her own body after cancer treatment, so that she might get pregnant with her husband through sexual intercourse, also seems likely to meet with Vatican approval.

Perhaps the greatest contribution that the Catholic Church can make to discussions about ethics and oncofertility is its emphasis on the importance of thinking about the context of procreation – even if not everyone agrees with the Vatican about what that context ought to be. Research in new reproductive technologies, informed by the Catholic Church, may take a greater interest in increasing an individual's or couple's ability to decide how, when, and with whom to procreate, rather than focusing primarily on an individual's or couple's decision *whether* to procreate.

## Evangelical Christianity

When exploring Evangelical Christian insights into the ethics of oncofertility, it is important to bear in mind Allen Verhey's observation that "there is no unanimity about what an 'evangelical' is, not among those who apply the term derisively nor among those who accept the label happily" [4, p. 77]. However, Verhey *did* identify three characteristics that apply to evangelical groups, whichever way they are defined: "the primacy of the Bible and its authority, the importance of a personal relationship to Jesus the Christ as Savior and Lord, and the necessity of living one's whole life in the light and power of the good news, the evangel" [4]. Alternatively, David Bebbington applied the following four characteristics to Evangelical Christianity: "conversionism, the belief that lives need to be changed; activism, the expression of the gospel in effort; biblicism, a particular regard for the Bible; and crucicentrism, a stress on the sacrifice of Christ on the cross" [5].

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[1] Special thanks are owed to Rachel Katz, one of the undergraduate students in Laurie Zoloth's winter 2008 Religion and Bioethics class, for this suggestion.

The National Association of Evangelicals (NAE) boasts 60 denominations as members [6]. Consequently, Evangelical Christian interpretations and assessments of oncofertility research and technologies may vary among denominations and even among congregations within a single denomination. Drawing upon perspectives from within the Assemblies of God and the Southern Baptist Convention as two communities within the Protestant traditions will help demonstrate the effect of this diversity on Evangelical Christian assessments of oncofertility.

The Assemblies of God and the Southern Baptist Convention share three guiding values that are particularly relevant to discussions about bioethics, oncofertility, and ART. First, both denominations emphasize the literal or plain meaning of Scripture, which includes the Old Testament and the New Testament. Second, both denominations uphold the belief that human life begins at the moment of conception – the moment sperm and egg unite to form an embryo. Finally, both denominations teach that reproduction and procreation should only occur in the context of a marriage between one man and one woman. Yet despite these common principles, Assemblies of God and the Southern Baptist Convention sometimes reach different conclusions about the ethics of ART.

Although it has not issued an official stance on whether and how it is appropriate to attempt to overcome infertility, the General Council of the Assemblies of God has expressed "concern that procedures tampering with the human embryo. . . have the potential to circumvent the sovereign will of God." Recourse to medical solutions is not prohibited; however, medical interventions should only be utilized after prayerful determination that it is God's will that the couple turn to reproductive medicine. Couples facing infertility are encouraged to ask "church leaders. . . to pray over and with them" that they will naturally conceive; persistent infertility should occasion further prayer, to determine whether God's plan for the couple involves a mission or task they could not accomplish with children. If no higher purpose for the infertility is determined, "surgical repair of blocked or damaged fallopian tubes or the careful administration of drugs to stimulate ovulation (when physical problems can be corrected by these means) would seem acceptable." ART must only be used to initiate a pregnancy within the context of marriage; technologies that involve a third party in the procreative process, such as artificial insemination by donor or the use of a gestational surrogate, are considered violations of the marital bond [7].

Christina H. M. Powell, an Assemblies of God pastor and trained research scientist, identified three principles that should guide decisions about the use of reproductive medicine: "respect for the beginning of human life," "respect for the marital bond," and "respect for the needs of the next generation" [8]. Powell expressed ethical concerns about in vitro fertilization not only because it separates the moment of conception from the loving sex act of a married couple, but also because makes pre-implantation genetic diagnosis (PGD) possible; PGD does not adequately respect new life as a gift from God [8]. Using donor eggs, donor sperm, or gestational surrogates is also morally suspect, because it introduces third-party involvement in an act that is supposed to occur between – and *only* between – husband and wife. Assemblies of God churches interpret the biblical story of Abraham, Sarah, and Hagar as a cautionary tale about the relational stress and dangers that can result from surrogacy [7, 8]. Posthumous reproduction, which removes procreation from the marital sex act *and* deprives the child of one of his or her genetic parents, is also ethically problematic because it violates the principles of respecting the marital bond and respecting the needs of the next generation. Powell cited Romans 7:2,

> For example, by law a married woman is bound to her husband as long as he is alive, but if her husband dies, she is released from the law of marriage,

as "clear [proof] that the marital bond dissolves at the death of one's spouse" [8]. She also noted that although a child's birth after the father's death has always been a possibility, posthumous *conception* is comparatively novel and especially problematic [8]. Thus, patients belonging to an Assemblies of God Church may be particularly concerned about ensuring that their cryopreserved gametes are not used to create a child after they or their partner die, and the Church or its members might advocate universally banning the use of cryopreserved gametes or tissue samples for posthumous reproduction.

However, Powell also listed up-and-coming oncofertility techniques – egg freezing and especially cryopreservation and later re-implantation of ovarian tissue – as potentially permissible techniques by which women, including and notably cancer patients, may preserve their fertility, since these technologies make it possible for a married couple to attempt procreation through sexual intercourse [8]. Couples or individuals who adhere to the beliefs of the Assemblies of God may turn to prayer before utilizing cryopreserved tissue or oocytes in order to ensure God has not assigned them a mission they could not fulfill with children.

Southern Baptist discussions about ART, in contrast, do not express much concern about separating procreation from a married couple's sex act. While the use of donor sperm, donor eggs, or gestational surrogates may be ethically problematic, using donated embryos does not appear to be prohibited. Information about "embryo adoption" – whereby one couple adopts and gives life to another couple's "leftover" embryo – is available on the Southern Baptist Convention's official website [9]. Southern Baptist concerns about IVF center upon the destruction of excess embryos. This moral apprehension is highest with regard to couples who turn to IVF *despite* knowledge that each IVF cycle usually involves creating more embryos than will be implanted [10, 11]. The Southern Baptist Convention, like the Assemblies of God, may be expected to approve of ovarian tissue cryopreservation and re-implantation. But the Southern Baptist convention may also embrace oocyte cryopreservation or in vitro follicle maturation insofar as these technologies, if successful, might allow fertility specialists to fertilize only as many oocytes as will be implanted in a particular IVF cycle. However, the large numbers of frozen embryos already in existence may prompt the Southern Baptist Convention to encourage members to adopt embryos otherwise destined for destruction, rather than pursuing oncofertility technologies to ensure their own genetically related progeny.

One contribution to discussions of oncofertility that comes from within Evangelical Christianity is the Assemblies of God's notion that reproduction and procreation are not necessary for living fulfilling, purposeful lives. In particular, the notion that God may assign couples tasks that they cannot accomplish unless they do not have children introduces an interesting alternative to two divergent attitudes, both of which may make the communal or societal lives of childless couples difficult: (1) that infertile couples remain childless because God is punishing them and (2) that couples who choose not to have children, especially despite technological advances that might provide reproductive success, are necessarily selfish or self-absorbed.

## Islam

Islam can be divided, at a minimum, into two main schools of thought: Sunni and Shi'ite. In his testimony before the United States' National Bioethics Advisory Council, Abdulaziz Sachedina cautioned that the Sunni majority and Shi'ite minority "do not represent an Orthodox/Reform divide" [12, p. G-3]. Sachedina suggested thinking of both Sunni and Shi'ite Islam as "'orthodox' in the sense that both base their arguments on the same set of texts that are recognized as authoritative by all of their scholars" [12, p. G-3]. These texts include the Qur'an, understood as the direct word of Allah (God), and the Sunnah, examples from the Prophet Muhammad's life included in scripture [13]. "Nonbinding but authoritative Islamic religious proclamations called *fatwas"* [14, p. 431], issued by Islamic legal scholars, also belong to the textual milieu of Muslim bioethics.

It is difficult to identify monolithic opinions even within Sunni or Shi'ite Islam. Differences in opinion or practice may result from a particular religious community's geographic location or local custom. Community opinions and customs may also be influenced by whether the community is situated in a state that governs by Islamic law. *Ijtihad*, understood as "the law of deductive logic" [13, p. 73] or "a form of individual religious reasoning," has led to a great diversity of opinion among Shi'ite Muslims in particular [14, p. 435].

Marcia Inhorn identified three main concerns driving ethical analysis and use of ART in Muslim communities in Egypt and Lebanon: (1) marriage; (2) incest; and (3) kinship and family life [14]. Reproduction must occur within the context of a marriage, traditionally defined between a man and a woman. While artificial insemination using sperm from a woman's husband and IVF utilizing the egg and sperm of husband and wife to create embryos that will be implanted into the wife are both permitted, the use of donor eggs, donor sperm, donor embryos, or surrogates is considered adulterous according to Islamic law [13–15]. A 1980 *fatwa* issued by The Grand Shaikh of Al Azhar University in Egypt, still used as a guideline in much of the Sunni *and* Shi'ite Muslim world, is understood to permit embryo cryopreservation; however, neither partner may use the embryos after the marriage comes to an end, whether by divorce or by the death of a husband or a wife [14]. Thus, technological advance in oocyte cryopreservation and in vitro follicle maturation may be of particular interest to unmarried Muslim women who, due to religious commitments, will not use donor sperm to ensure their own fertility preservation.

Abul Fadl Moshin Ebrahim argued that if infertility is considered a "defect" or "disease," then the statement attributed to the Prophet Muhammad, "for every disease there is a cure," would allow Muslims to turn to medicine to overcome infertility [15, p. 100], particularly oncofertility patients whose infertility results from cancer or cancer treatment. Oocyte cryopreservation and in vitro follicle maturation technologies may be especially appreciated in Muslim communities abiding by the Qur'an's prohibition of "legal adoption as it is known in the West, whereby a child takes its adoptive parents' surname and is treated as one's own child" [14, p. 441]. Inhorn observed that in the Muslim world, even when adoption is legal, it is often discouraged [14]. The prohibition of adoption is tied to Qur'anic passages that teach the importance of knowing one's personal familial lineage. As A. R. Gatrad and A. Sheikh succinctly stated, "Children have the right to be born through a valid union (marriage) and to know their parentage fully" [13, p. 73]. Inhorn noted that "preserving the 'origins' of each child – meaning its relationship to a known biological mother and father – is considered. . . a moral imperative" [14, p. 440]. Without knowledge of one's lineage there is "potential for incest among the offspring of unknown donors," which is of great concern in many Muslim communities [14, p. 440]. Another concern, particularly in communities or states governed by Islamic law, is that children may only inherit from their biological parents. Because oncofertility technologies would enable Muslim couples to create children who are the genetic offspring of both partners, and particularly because these technologies open procreative opportunities for individuals who might otherwise lack a viable procreative option – particularly unmarried Muslim women – it is possible that Muslim patients and Muslims in general may embrace oncofertility technologies for fertility preservation, as long as reproduction occurs in the context of marriage and without the involvement of a third-party donor.

Islam's proscription of adoption invites reflection about the significance of genetics in the relationship between parent and child – reflection that may deepen discussions about the ethics of oncofertility, and the ways these technologies may change interpersonal relationships in different societies. Additionally, Muslim concerns about inheritance provide an important reminder of the challenges that new reproductive technologies may pose to our legal systems.

The scholars of Islam in this volume offer still another perspective. New receptions and interpretations of the Qur'an allow new reflection on families and children, economic relationships, and the role of women in the faith communities of Islam.

## Judaism

Anticipating or formulating Jewish responses to oncofertility research and technologies is complicated by Judaism's canonical inclusion of multiple, often conflicting legal and interpretive positions. There are several distinct branches of Judaism: Reform, Conservative, Orthodox (including Modern Orthodox and Haredi/Ultra-Orthodox varieties), and reconstructionist, each with their own rabbinic training programs and councils which offer arguments and policies to their respective congregations. Even within each of the branches of Judaism, a plurality of interpretations and stances is preserved as legitimate, though communal norms may affect which interpretations a particular community, congregation, or individual embraces.

Although each branch of Judaism ascribes different degrees of authority to Judaism's canonical texts – the Torah, Midrash, Mishnah, and Talmud – these texts form a common foundation of Jewish ethical discourse. Aaron Mackler delineated four guiding values in Jewish reproductive ethics: (1) "respect for persons," (2) "procreation," (3) "human stewardship," and (4) "healing," each of which can be traced to canonical texts [16, p. 321]. For instance, respect for persons derives from Genesis 1:28 – which states that human beings were created in the image of God – as well as later rabbinic interpretations and applications of this concept [16, 17]. The value of procreation also derives from Genesis 1:28 – the first command God gives to human beings is to "be fruitful and multiply." Rabbinic sources thus interpreted procreation as a duty, albeit a duty for men, not for women [18]. Many female scholars of Judaism have noted the complex history surrounding women and reproductive duties, in which women are enjoined to respond to the crisis of infertility throughout the Torah narrative, but whose choices to do so are not necessarily considered normative. The halakhah preserves commentary about the need for limits on reproduction, on alternate ways of fostering children, and on the permissibility of non-reproductive sexuality (see Zoloth in this volume). Dena Davis has written extensively about the need for feminist considerations of actual practices of clinical care to be considered when we relate the Jewish positions on fertility [19]. Additionally, Elliot Dorff asserts that "the commandment to procreate only applies to having children through sexual intercourse" [17, p. 399]. The duty to reproduce does not apply to infertile couples; Jewish law cannot obligate anyone to utilize ART [17]. However, some Jewish commentators and communities place an especially high value on procreation because 6 million Jews were murdered in the Holocaust, and thus some infertile Jewish couples may feel social or familial pressure to reproduce, even if they are not obligated by *halakhah*, Jewish law, to do so. Mackler describes human stewardship as "reverent but active partnership with God in completing the works of creation and improving the world," which is closely connected to the fourth value, healing, frequently understood as "[restoring] that which has been lost" and "not [standing] idly by the blood of one's neighbor" [16, p. 321]. Thus, oncofertility, insofar as it aims to restore patients' lost fertility – especially fertility lost prematurely because of cancer or other medical treatment – might easily be assimilated into Jewish notions of the duty to heal.

Embryos, fetuses, and fully developed human beings possess different – and increasing – moral statuses according to *halakhah.* Rabbinic literature describes a fetus less than 40 days old as "merely water," while a fetus more than 40 days old is treated "like the thigh of its mother" [20, p. 313]. Dorff explains that the prohibition against self injury prohibits a human being from amputating his or her healthy leg, but "if one's thigh had become gangrenous, and if the person were likely to die if the leg were not cut off, then amputation of the leg would not only be permitted, but required, for we have the duty to preserve our life and God's body" [20, p. 313]. Thus, he concludes, "abortion is generally prohibited according to Jewish law, not as an act of murder (the fetus is not a full-fledged person), but as an act of self-injury" [20, p. 313]. Contemporary halakhic interpretations do not ascribe moral status or rights to an extracorporeal embryo – which enables widespread Jewish acceptance of ART, including IVF and embryo cryopreservation [20].

Anxieties within Jewish scholarship center not on concerns about technology, but about the creation of families in a way that validates other norms. An important caveat to widespread *halakhic* and practical acceptance of ART is that reproduction and procreation are intended to occur within the context of marriage. Within Orthodoxy, marriage only refers to relationships between a man and a woman. The Conservative and Reform movements possess a variety of stances on same-sex marriage, ranging from rejection, to approval of civil but not *Jewish* same-sex marriages, to acceptance of same-sex marriages as Jewish. This generally means that ART should only be utilized by married couples, however defined. Some Orthodox authorities require couples to use only their own gametes, which precludes AID [17, 21]. The use of donor eggs is *halakhically* less problematic, since the mother is *halakhically* defined as the woman who physically gives birth to the child, but the father is defined as the source of the sperm [21]. The Conservative and Reform movements are more lenient regarding the use of donor sperm, since, as Dorff explains, "the biblical ban on adultery is violated only when there is contact of the genital organs of the two people having the affair" [17, p. 394]. However, some Conservative rabbis require the husband's consent before donor sperm is used [21]. Depending upon the particular rabbi or Jewish community in question, oncofertility technologies may be used to assist procreative efforts of same sex couples.

Jewish sources are unlikely to raise any objections to oncofertility technologies, though Jewish scholars and rabbis may favor restricting the use of cryopreserved oocytes or in vitro matured follicles to the procreative efforts of married couples. The approval of so many ART by such a wide variety of rabbis makes the need for oocyte cryopreservation or in vitro follicle maturation less urgent, but these technologies may be particularly welcome within Jewish communities whose religious authorities prohibit the use of donor gametes, since these techniques offer an unmarried individual the opportunity to preserve their fertility so they may procreate with their future spouse.

The context of oncofertility is important; while the technologies may be used for a variety of women facing infertility for a variety of reasons, the loss of fertility from cancer or cancer treatment resonates strongly with Jewish ethical imperatives to restore or preserve lost property. One *halakhic* definition of healing – restoring that which someone has lost – can direct conversations about oncofertility to considerations of the field's reason for being: not only do some patients become infertile because of cancer, but many patients also become infertile because of the treatments used to cure the cancer. It may be useful to conceptualize reproductive assistance to these patients as an extension of the healing responsibilities assumed from the moment cancer treatment is prescribed. This notion also offers a thought-provoking model for thinking about the ethics of medical side effects. The second definition of healing – not standing idly by the blood of one's neighbor – may help highlight the preventive aspect of oncofertility research. Oocyte cryopreservation, in vitro follicle maturation, and ovarian tissue cryopreservation and re-implantation are designed to *prevent* a crisis of infertility which might occur for some patients once they learn they cannot reproduce with their own gametes.

## Hinduism

The colonial construction or "invention" of Hinduism as a unified religion makes it particularly difficult to talk about Hindu bioethics. Swasti Bhattacharyya, who has written about Hindu bioethics, cautions that "the term 'Hindu'... is a foreign label for a rough collection of related, yet quite diverse, social, religious, cultural, and philosophical traditions originating from within India" [22, p. 5]. Nevertheless, because the term's introduction has shaped the self-identification of adherents to the many traditions that fall under the umbrella of Hinduism, and because these traditions share a textual canon and some common history, it may be possible to sketch a few principles and interpretations that, taken together, suggest the outlines of Hindu bioethics and demonstrate some common touchstones for Hindu bioethical discourse. Hinduism's sacred texts are of two varieties, revealed and traditional. Revealed texts include the *Vedas* and the *Upaniṣads*; among the traditional texts are the *Law Book of Manu* and two epic literary narratives, the *Ramayana* and the *Mahābhārata* (which includes the *Bhagavad Gītā*) [22]. In her exploration of Hindu bioethics, Bhattacharyya suggested an ethical framework grounded in the traditional literature, especially the *Mahābhārata*, for thinking about ART [22]. In particular, she drew upon three "birth narratives" which describe the efforts by which Kunti, Mādrī, and Gāndhārī, three queens, ensure that they will have children and that the Bharata family lineage will continue. Bhattacharyya argued that

> the epic... reflect[s] a shared experience in the struggle against infertility and a shared attitude of openness and creativity towards procreation. Trying to fulfill their desires to have children, the narrative depicts how the three queens overcome major obstacles by utilizing creative and magical means. Today, the creativity is expressed through various forms of reproductive technology [22, p. 3]

Within these narratives, Bhattacharyya identified practices of sperm donation, including post-mortem sperm donation; gene selection; adoption, including adoption by which one wife becomes the mother of another wife's children; artificial wombs; and "paternal surrogacy," a phrase she uses to describe acts in which a married woman has sex with another man or a god in order to provide that union's offspring as an heir for her husband [22].

Bhattacharyya identified six characteristics that pervade Hindu thought: "(1) an emphasis on the centrality of societal good; (2) a firm belief in the underlying unity of all life; (3) the expectations and requirements of *dharma*; (4) the multivalent nature of Hindu traditions; (5) a theory of *karma*; and (6) a commitment to *ahisā* (no harm)" [22, p. 63]. From these characteristics, it is possible to derive principles and concepts that shape a Hindu bioethic. These include but are not limited to (1) the importance of having children, including the importance of having a son; (2) a broad notion of family; (3) the value of family planning; and (4) that ethical considerations should focus on the specific details of individual cases. Hindu tradition divides the human life into four stages: student, householder, "forest-dweller," and renouncer. The *Law Book of Manu* identifies the householder stage, which entails "establishing one's economic stability, getting married and having children," as the most important, because the householders support society's students, "forest-dwellers," and renouncers [22, p. 64]. Traditionally, individuals may not pass from the householder stage to the "forest-dweller" stage until they have had grandchildren – more specifically, grandsons [22]. Hindu tradition places great importance on childbearing. However, it would be inappropriate, according to this framework, to attempt to give birth to and raise children while one is not only in the student stage but also in the "forest-dweller" or renouncer stages. This notion – that childbearing and rearing should be limited to a particular, proper stage in the human life span – contributes a thought-provoking backdrop for discussing teen pregnancy, as well as men and women past normal reproductive age who want to use ART to have a child.

There may be interpretations from within the Hindu tradition that not only permit but strongly encourage using ART to have a child, particularly when a couple has had difficulty conceiving, and especially to have a son. However, traditional Hindu conceptions of family extend beyond the nuclear family of parents and children to include aunts, uncles, and in-laws; adoptive relatives; grandparents; close friends – even all the members of the town in which an individual was raised [22]. Additionally, because children need not be genetically related to their fathers to count as heirs, and because children may be considered sons (or daughters) even if they are not eligible to be heirs, members of some Hindu communities may be less likely to pursue the technological interventions at their disposal, since lineage does not depend upon a genetic tie between parents and children. Despite the fluid notions of family present in Hindu texts, however, anthropological studies suggest that childless women in India experience social stigma and decreased stability in household relationships [23]. Thus, women who can afford to utilize ART may feel social or familial pressure to do so.

Hindu thought, with its focus on individual cases and circumstances, can contribute to the ethical discourse surrounding oncofertility by shifting attention away from the technologies themselves and onto the individuals considering whether or not to use them. It may not be ethically responsible for every individual with frozen tissue, gametes, or embryos at their disposal to use them for reproduction *even if* ovarian tissue cryopreservation or in vitro follicle maturation is prima facie unproblematic. This proposition – that access to "licit" ART need not translate into actually using them – has an important role to play in helping to change the experiences of many individuals and couples for whom the mere possibility of utilizing ART may be felt as a coercive or oppressive expectation – by society, family, or fertility specialists – that these technologies *will* be used. Additionally, the varied and complex families presented in the *Mahābhārata* narratives challenge us to more seriously consider non-genetic and genetic children as morally and meaningfully equivalent, and to question whether society has become overly fixated on genetics as the glue that bonds family members together.

## Buddhism

Buddhism “is characterized by a devotion to ‘the Buddha,’ ‘Buddhas,’ or ‘Buddhahood,’” where Buddha not only refers to the historical Buddha but also operates as “a descriptive title meaning ‘Awakened One’ or ‘Enlightened One’” [24, p. 3]. There are two main “styles” of Buddhism – Theravāda and Mahāyāna; Mahāyāna Buddhism includes multiple schools of Buddhism, such as Zen, Pure Land, and Tibetan Buddhism [25, 26]. The variety of schools, coupled with their development in so many different socio-cultural settings, makes it difficult to speak about a singular Buddhist bioethic. Nonetheless, Peter Harvey suggested that the Four Noble Truths form part of a common ground for the many varieties of Buddhist ethics [24]. The Four Noble Truths teach that

> (1) life is ultimately unsatisfactory (*dukkha*); (2) life’s unsatisfactoriness stems from desire (*tahā*); (3) enlightenment or nirvāa (*nibbāna*), what the Buddha himself had attained, is the elimination of desire and unsatisfactoriness; and (4) nirvāa is cultivated by following the Eightfold Path [26, p. 63]

Another important concept is *samsara*, or the cycle of rebirth, which Buddhists believe all living beings endure until they achieve enlightenment and break free from this cycle. The law of *kamma* (*karma*) determines the life into which any being is reborn: “beings are reborn according to the nature and quality of their actions” in their previous life [24, pp. 14–15]. The effects of the law of *kamma* may also be felt in one’s current life [24]. Shoyo Taniguchi described *kamma* as a natural law of “cause and effect, of action and reaction” [27, p. 77]. Buddhist concern for suffering and its alleviation is connected to the concept of *kamma*. Actions which harm oneself and/or others are “unskillful” actions; actions which either benefit or do not harm oneself and/or others are “skillful” actions [27]. Buddhists are encouraged to act skillfully and avoid unskillful (i.e., harmful) actions [27].

Buddhist ethics can be divided into two strands: monastic ethics and householder ethics [26]. According to Harvey, “Buddhism has traditionally held celibate monasticism in the highest regard, but it has also seen marriage and family life as highly suitable for those who cannot commit themselves to celibacy,” although he noted at least one strain of Western Buddhism that is sharply critical of the householder lifestyle [24, p. 103]. The Sigālovāda Sutta, “a key text for lay Buddhist ethics, including sexual ethics” [26, p. 68], may be particularly relevant to Buddhist reproductive ethics and reflections upon ART.

Some Buddhist schools or scholars might encourage, or at least accept, oncofertility research because it aims to alleviate the additional suffering that patients may feel when they learn not only that they have cancer but also that the cancer and/or its treatment may prevent them from reproducing in the future. ART, including the techniques under development by the Oncofertility Consortium, may alleviate the suffering some couples or individuals experience as a result of their infertility. Shoyo Taniguchi suggests that “as long as technology brings benefits to the couple who wishes to have a child, and as long as it does not bring pain or suffering to any parties involved, Buddhism would find no conflict in applying and using modern technology" [27, p. 80]. But some Buddhist schools or scholars might criticize oncofertility and ART for perpetuating the disillusioned attachment to this life which sometimes motivates human beings' reproductive desires. Although ART may remove the physical and bodily desires of sex from the reproductive process, the mental or emotional desire for a child can be equally problematic. Some monastic texts, such as the Vinaya Ptaka, equate the desire for a child with the desire for wealth and economic security – desires which lead humans astray from the path to Enlightenment [26]. Additionally, "the *Dhammapada* declares that delusion makes one say that one's body belongs to oneself or one's child belongs to oneself" [27, p. 78]. A genetically related child can no more belong to a parent than a non-genetically related child. Some Buddhist thinkers may, therefore, eschew ART for exacerbating disillusioned notions about the parent–child relationship (which might, arguably, be harmful to both parent and child). This criticism is especially relevant regarding the techniques central to oncofertility research, which aims to ensure that infertile men and women may have genetically related offspring.

Even Buddhist arguments supporting oncofertility research and the use of ART are unlikely to approve of *all* reproductive technologies. According to the *Mahātahāsakhaya Sutta*, human life begins at conception, understood today as the fusing of sperm and egg *and* the embryo's animation by a soul that was awaiting rebirth [25, 27]. Since it is impossible for humans to determine whether a soul is present in a particular embryo, concerns about avoiding unskillful actions might encourage erring on the side of caution and treating all embryos as though they contain a soul; embryos thus have a right not to be harmed [27]. Disposing of leftover embryos at the conclusion of an IVF cycle is, therefore, ethically problematic; additionally, Damien Keown has suggested that embryo research would be unacceptable because it subjects embryos to harm and/or destruction without their consent [25]. Keown also argued that freezing embryos is problematic since so many embryos do not "survive" the thawing process [25, p. 137]. Buddhist principles would seem to require fertilizing only as many eggs as will be implanted in a particular IVF cycle.

However, Tanigushi noted that even in early Buddhism, sperm and unfertilized eggs were not granted the moral status of living human beings themselves [27]. Thus, oncofertility research into oocyte cryopreservation and in vitro follicle maturation may be characterized as the development of "skillful" ART, though the aforementioned limitations on fertilizing eggs would still apply. Oocyte cryopreservation or in vitro follicle maturation might actually be among the most ethically responsible forms of fertility preservation, from a Buddhist perspective.

Buddhism can contribute to larger discussions about oncofertility and ethics by challenging the tendency, so prevalent in the West and latent in the drive to develop new infertility treatments, to privilege biological over non-biological offspring. Additionally, Buddhist ethics emphasize harm as the yardstick against which an action's morality is measured. The relevance of motivation to determining whether an act is harmful – for instance, procreation as an attempt to "possess" offspring or satisfy the physical desire to experience pregnancy would likely be considered harmful – may refocus discussions about fertility preservation in an important way. Rather than focusing solely on the fact that there are patients who have expressed interest in fertility preservation, Buddhism may encourage exploring and reflecting upon the motivating factors that drive patients to pursue fertility preservation, as well as the effect these motivating factors may have on society as a whole.

## Conclusion

This chapter provides an overview and a brief introduction to six religious traditions and their potential contributions to discussions about the ethical issues surrounding the new field of oncofertility. More research, including ongoing research on how clergy respond to actual cases should oncofertility research prove fruitful, is needed. Far from the final word on the matter, these outlines are intended to provide the beginnings of multivocal contributions from religion to the exploration of ethics and oncofertility. Each religious tradition discussed herein – Catholicism, Evangelical Christianity, Islam, Judaism, Hinduism, and Buddhism – contains multiple and distinct perspectives. These viewpoints can complement, converge with, or challenge the philosophical, psychological, anthropological, medical, and legal perspectives included in discussions of bioethics. We hope that the examples of how each tradition may alter the terrain of the discourse on ethics and oncofertility demonstrate not only why each tradition is worth considering on its own but also the more vibrant, complex, holistic picture of the oncofertility project that emerges when these and other religious traditions are all included as participants in the conversation. It is not enough to place these religious perspectives side by side – not enough to note, for example, that not only Islam and Hinduism but also Buddhism, suggest dramatically different attitudes toward adoption. Rather, we might make this observation the epicenter of an inquiry into the different conceptions of family and parent–child relationships that inform these and other attitudes toward adoption, weighing these theories of family ties against anthropological and sociological studies of adoption – information that, together, allows more complex, nuanced assessments of how oncofertility may alter or be altered by conceptions of family and perspectives on adoption. Discussions are richer and the picture fuller when multiple perspectives from multiple religious traditions are brought into conversation with one another so that we may probe the roots and implications of agreements and disputes among them.

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# Chapter 21
# Sacred Bodies: Considering Resistance to Oncofertility in Muslim Communities

**Rumee Ahmed**

## Introduction

It has been correctly stated that the religion of Islam is defined by orthopraxy rather than by orthodoxy. That is, it is more a religion of practice and law than a religion of doctrine. In the absence of a central church, Muslims rely on legal scholars to define the acceptable parameters of Islamic practice. These scholars may come to disparate conclusions and define different modes of practice for discrete communities and still be considered genuinely "Islamic." Thus, the practice of Islam in various locales often differs based on the leanings and predilections of the legal scholars in that area. The situation is further complicated by the fact that Muslims are not bound to follow any particular scholar or groups of scholars, but rather may choose to follow, or not follow, whomsoever they wish. The result is that Islamic practices – along with definitions of permissibility and impermissibility – are variegated and diverse, resisting any attempt to portray Islam as a monolithic structure and incapacitating anything so reified as "Muslim Thought."[1]

For a medical practitioner, then, the appellative "Muslim" yields only limited information about a patient's beliefs, practices, or level of religiosity. It may be that a Muslim patient adheres to one of many legal schools of Islamic thought or none at all. In matters related to oncofertility, one can never be entirely certain of a patient's affinity for legal scholarship that approves of or frowns upon the practice of oncofertility. That having been said, Muslim legal scholarship has been, in general, exceedingly accommodating in matters of assisted reproductive technology. Since oncofertility is a new enterprise, there is no legal literature on the subject, but we can surmise that legal scholars will accord it a treatment similar to that given to other modern medical reproductive interventions.

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On matters of reproductive technology such as in vitro fertilization, stem cell research, and frozen embryos, Muslim jurists have been, on the whole, very obliging. Abdul Aziz Sachedina in his important book, *Islamic Biomedical Ethics*, recounts legal discussions on reproductive technologies and juridical approaches to many medical issues. He finds that jurists often make recourse to foundational principles that would justify a particular medical innovation as acceptable within Islamic law. Two of these principles are operative in most cases, namely the principle of necessity (*ḍarūrah*) and the principle of "no harm, no harassment" (*lā ḍirar wa lā ḍirār*).[2] That is, if a medical procedure was deemed necessary for the patient's well-being – regularly defined in terms of functionality and quality of life – and did not cause harm to the patient or others, then the procedure was deemed legally licit. Sometimes jurists put parameters around the proper use of these reproductive technologies or confined them to specific circumstances, yet they allowed that the practice itself was not to be censured.[3] There is reason to believe that Muslim jurists will apply these same principles to the practice of oncofertility. They would likely argue that because it is necessary to maintain the reproductive functionality of a cancer patient and because oncofertility does not cause harm to an independently viable human being, then the practice is acceptable under Islamic law.

Interestingly, these legal discussions will likely not be overly concerned with the larger theological issues that oncofertility might raise. Generally speaking, theology does not figure prominently in legal discussions since it is assumed that humans cannot mimic God or impinge on God's sovereignty. Thus, by definition, the result of human action cannot be theologically problematic. Dr. Sachedina cites the prominent Muslim jurist Yūsuf al-Qaradāwī saying, "... no one can challenge or oppose God's will. Nothing can be created without God's will facilitating its creation. As long as humans continue to do so, it is the will of God. Actually, [jurists] do not raise the question whether it is in accord with the will of God. Our question is whether the matter is licit or not."[4] This suggests that theological concerns would not impede a significant number of Muslim jurists from approving of oncofertility as a legally acceptable practice.

It is instructive, however, to examine dissenting opinions on biomedical issues that tap into principles that may extend beyond the legal purview. Jurists who issue opinions sanctioning certain medical procedures relevant to oncofertility tend to rely on the principle, "the body belongs to God." In this vein, they argue that the inviolability (*ḥurmah*) of the body is paramount,[5] and unless there is a dire need that cannot be met through any other method, medical procedures should not alter the body in any way. This principle is most often evoked in discussions of organ transplantation and autopsies, but can apply any time a part of the body is removed, altered, or damaged. This is relevant to oncofertility since ovarian tissue is removed

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[2] Sachedina AA. Islamic biomedical ethics. Oxford: Oxford University Press; 2009:111–113.

[3] Ibid., 214

[4] Ibid., 201

[5] Ibid., 195

in order to cultivate viable eggs. There is evidence to suggest that this principle of the *ḥurmah* of the body is particularly beholden to many Muslim communities across the world. I suggest that this is so because it neatly extends from the dominant Muslim narrative about the origins and ultimate end of the body itself.

## The Narrative of Bodily Inviolability

The creation story as described in the Qur'ān is oft repeated in Muslim communities, schools, and pulpits. In pre-history, God determined to create a representative on Earth who would abide by His command.[6] To that end, God fashioned a being out of clay with His own hands and perfected that being. There are multiple verses in the Qur'an that testify to the pristine nature of this being as God's greatest and most perfect creation.[7] From the perspective of the body, it was ideally proportioned and free from any defect. Further, God imbued this creature with the knowledge of right and wrong such that it had an internal balance by which it could discern the moral rectitude of its actions.[8] As His masterstroke, God breathed into this being His Spirit, which elevated this being further.[9] God named the being "Adam" and taught him the names of all things.[10] As a representative of God, Adam was charged with maintaining his body, of which he was merely a custodian.

Adam lived in a garden with his mate, Eve.[11] There they had all that their hearts desired. We know of only one rule that they were required to follow, which was that they were not to eat fruit from a certain tree. They initially abided by this law, but a jealous creature made of fire, Satan, tricked them into eating from the tree. Satan encouraged them to eat the fruit by exploiting a legal loophole and saying, "I am a sincere advisor unto you." Upon eating the fruit, Adam and Eve's nakedness became apparent to them and they rushed to cover their shame. They then had to contend with God, who did not dismiss their transgression. Instead, God banished Adam and Eve to Earth, where they were forced to toil for their livelihood. God promised them, however, that He would send them guidance upon which they could base their lives. This guidance corresponded to the internal balance of right and wrong that God placed in all humans. Hence, the children of Adam would be able to recognize the guidance when they saw it and would be able to make sophisticated decisions by combining this guidance with their internal moral compass. If any of Adam's progeny followed the guidance and worked righteously, they would be saved; but if they failed to do so, they would be damned. Adhering to God's guidance would

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[6] Qur'ān, 2:30

[7] Q. 3:33, Q. 64:3, Q. 95:4

[8] Q. 91:8

[9] Q. 32:9

[10] Q. 2:31

[11] Several versions of this story can be found in the Qur'ān, including Q. 2:30–37; Q. 7: 11–25; Q. 20:115–125

restore any child of Adam to their original perfection, making them pure during their lives and saved in the hereafter.[12]

Each child of Adam will eventually die and be brought back to God in order to account for her/his deeds on Earth. To allow for a physical trial, God will restore the dead their bodies and they will literally stand in judgment concerning how their bodies were utilized.[13] Naturally, if given the chance one would attempt to highlight the good and downplay the bad of one's life, and so God will allow one's body parts to attest to their deeds on Earth.[14] The limbs and organs will speak to the extent to which their host, to whom they were given as a trust, used them in fidelity with and in defiance of God's guidance and the internal moral compass. God will then pass judgment and assign the individual to either heaven or hell.

There are three noteworthy aspects of this narrative with respect to the present discussion. The first is the pristine nature of the body at the point of creation and after the fall of Adam. The Muslim creation narrative views the human being as neither inherently sinful nor irredeemable. Rather, the human is in the same pristine form as at the point of creation and has the capacity to remain pristine in body and soul. It is an individual's actions that remove her from this hallowed position, whether through mutilation of the body or through morally repugnant behavior. Thus, any change to the body is considered a significant event, even when that change results in the improved health of the individual. That is not to say that any alteration of the body is inherently problematic, but that it is generally frowned upon unless there is a demonstrated necessity (*ḍarūrah*) for that alteration.

The second issue of note is Satan's justification for leading Adam astray. He argued that the letter of the law could be manipulated to allow for Adam to eat from the forbidden tree and added that he was a "sincere advisor."[15] This has led Muslim jurists to harbor a level of skepticism when any medical innovation appears to benefit a patient. There is always the possibility that a procedure looks beneficial when approached rationally and could be justified through legal manipulation, but may anger God by breaking His laws. Therefore, every medical issue must be considered beyond its apparent physical benefit, especially if it appears to be of benefit yet violates the *ḥurmah* of the body.

Third, the body is to be physically resurrected on the Day of Judgment in order to testify for and against the individual. If any part of the body is removed during life, especially if it is transplanted into another body, then there is some tension concerning the physicality of one's ultimate trial. Presumably, God would be able to find a way to mediate the matter, yet this very concern has led to negative views concerning organ transplantation, bodily mutilation, and cremation, not to

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[12] Q. 7:42–43

[13] Q. 75:3–4

[14] Q. 36:65

[15] Q 7:21

mention cadaveric research.[16] Each of the above noteworthy aspects of this narrative concerns the inviolability of the body and its status as a “trust” from God. Although these concerns are sometimes dismissed in juridical conversations in favor of other principles, they palpably affect the medical decision making and concerns of many Muslim communities across cultures.

## Beyond Jurisprudence: Widespread Muslim Attitudes Toward the Body

Several ethnographic studies have demonstrated that, despite juridical rulings to the contrary, Muslims are extremely wary of any medical procedure that violates the *ḥurmah* of the body. Organ transplantation has been a convenient method of measuring this phenomenon,[17] especially given that such donations are often the difference between life and death and that organ donation and transplantation have been approved by multiple Islamic juridical boards.[18] Despite being told that a family member may die without a donation and despite being told about juridical rulings that allow for organ transplantation, many Muslims have demonstrated a reluctance to donate.[19] This reluctance has been captured in multiple surveys throughout the Muslim world and Muslims living in non-Muslim majority countries,[20] as well as in ethnographic works such as Farhat Moazem’s excellent *Bioethics and Organ Transplantation in a Muslim Society: A Study of Culture, Ethnography and Religion*.

The reasons for the reluctance on the part of both organ donors and recipients vary, but they almost uniformly concern popular conceptions of the body as a pristine vessel from God. Some donors reported a desire to help, but a fear of corrupting themselves in the process. Some recipients felt a fear that they would be somehow weaker with a foreign organ.[21] Both donors and recipients expressed concerns about violating the order of the universe and being unsure about the testimony of their

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[16] See Ebrahim A. Organ transplantation: contemporary Sunni Muslim legal and ethical perspectives. Bioethics. 1995; 9:291–302.

[17] The discussion surrounding organ transplantation in legal debates is also helpful for elucidating the social factors influencing juridical decisions. See Hamdy S. Rethinking Islamic legal ethics in Egypt’s organ transplant debate. In: Brokopp J, Eich T, Eds. Muslim medical ethics: from theory to practice. Columbia: University of South Carolina Press; 2008:73.

[18] Shaheen FAM, Souqiyyeh MZ. Increasing organ donation rates from muslim donors: lessons from a successful model. Transplant Proc. 2004; 36(7):1878–79.

[19] Raza M, Hedayat KM. Some sociocultural aspects of cadaver organ donation: some recent rulings from Iran. Transplant Proc. 2004; 36(10):2888. Christian N. Challenging Islamic myth on organ transplants as ailments rise. New York Times. May 20, 2000:A9.

[20] Keçecioğlu N, Tuncer M, Yücetin L, Akaydin M, Yakupoğlu G. Attitudes of religious people in turkey regarding organ donation and transplantation. Transplant Proc. 2000; 32(3):630; Rachmani R, Mizrahi S, Agabaria R. Transplant Proc. 2000 32(4):757.

[21] Moazem F. Bioethics and organ transplantation in a Muslim society. Bloomington: Indiana University Press; 2006:166.

organs on the Day of Judgment.[22] These concerns have little to do with the structure and function of juridical and theological debates, but they have a tangible impact on the lives of patients. That is, although Islam may be a religion of orthopraxic legal discussion, sometimes the beliefs of the laity are independent of juridical debates.[23] Being comfortable with a medical procedure, it would seem, has less to do with having a juridical ruling authorizing the procedure and more to do with having a comfortable narrative within which to couch the procedure.

These attitudes toward organ transplantation have a direct bearing on oncofertility. The removal of ovarian tissue, regardless of its juridical permissibility, encroaches on the common anxiety about violating the *ḥurmah* of the body. When the tissue is removed, the patient might believe that they have distorted or mutilated the pristine body given to her as a trust by God.[24] Again, it should be noted that this is not the view of all Muslims, but appears to be a view espoused by a significant number of Muslim individuals. Nevertheless, this anxiety might in some circumstances be overcome if there was a demonstrated need (*ḍarūrah*) that necessitated the removal of ovarian tissue. In the case of oncofertility, the need is only potential and deferred. That is not to say that the need is not valid, but that it is harder to make the case that there is a pressing need to remove ovarian tissue as opposed to trying some other reproductive intervention at a later stage.

When making the case for oncofertility, the issue is further complicated because the concerns around removing an organ also go beyond the individual. The narrative that posits the inviolability of the body is itself situated in a larger community within which the patient is a member. These communities may cast judgment upon someone who is anomalous in their narrative worldview. In the case of organ transplantation, many men and women signaled a trepidation with the procedure because they might be seen as “less than,” or that their bodies are somehow compromised.[25] While this would be a concern for any member of a community, it is especially of concern to adolescents. Beyond the usual apprehensions about fitting in and excelling, adolescents are on the cusp of several life-defining moments, most notably marriage. Having survived cancer is a significant enough impediment to attracting marriage prospects, but having part of an organ permanently removed – whether or not that removal has any effect on a young girl’s health – is a stigma that may remain after the cancer goes into remission. This unfavorable attitude might result in the patient whose organ is removed having a lowered social status in the

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[22] Al-Khawari F, Stimson G, Warrens AN. Attitudes toward transplantation in UK. Muslim Indo-Asians in West London. Am J Transplant. 2005; 5(6):1326–31.

[23] Shaheen FA, Al-Jondeby M, Al-Khader AA. Important social factors that affect organ transplantation in Islamic countries. Exp Clin Transplant. 2003; 1(2):96–101.

[24] Altraif IH, Al-Sebayel MI, Nondo H. Knowledge and attitude toward organ donation among males in Riyadh, Saudi Arabia. Saudi J Kidney Dis Transplant. 1996; 7(2):135–8.

[25] Moazem F. Bioethics and organ transplantation in a Muslim society. Bloomington: Indiana University Press; 2006:164.

community. Hence, the removal of ovarian tissue in an oncofertility intervention may result in a stigmatization of the patient that, in turn, affects her future prospects and level of communal involvement.

## The Clinician's Burden

As stated earlier, Muslim attitudes toward organ transplantation and reproductive interventions are by no means uniform. There are some Muslims who do not share the narrative above, some who are guided by legal scholarship, and some whose Muslim identity does little or nothing to inform their decision making. There are some Muslim communities that do not have any stigma connected to organ removal. Some Muslim communities understand the *ḥurmah* of the body differently and might have no problem, juridical or otherwise, with the practice of oncofertility. How, then, is the clinician supposed to advise a Muslim patient? It is patently impossible for a clinician to know all the contours of a patient's beliefs – whether they be Muslim or not – or their community's relative influence. Moreover, a clinician cannot simply approach a community leader or chaplain for authoritative advice because the patient may not hold that voice to be authoritative. Thus, the clinician is put in a difficult position when discussing options with a patient. In order to consult with a patient about a particular form of reproductive intervention, the consultation might have to speak to a narrative that is not captured in legal discussions. To make the consent truly informed, the clinician might have to understand the quality-of-life issues that are subject to the community's understanding of the procedure. Above all, these narratives and quality-of-life issues vary from patient to patient.

The intent in describing the issues that may arise in response to oncofertility in certain Muslim societies is to introduce the personal issues that may accompany oncofertility in some persons and communities.[26] These issues might not be readily apparent and may not be addressed by the sayings and rulings of authority figures. This requires that the conversations about the optimal reproductive intervention for adolescent cancer patients involve multiple parties and an informed hospital staff concerning some of the *possible* issues that may surround a particular procedure. Obviously, these conversations cannot always occur in time for the patient to make a fully informed decision, which underscores the need to garner input from multiple stakeholders prior to the actual interaction between the patient and the clinician.

Having access and familiarity, if not an intimate knowledge, of the myriad narratives that may be operative not only enriches the conversation between the clinician and patient but also allows for a genuine dialogue between the two. The clinician may attempt to ascertain and enter the narrative of the patient through conversation

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[26] Some of these potential issues are raised in Shaheen FA, Al-Jondeby M, Kurpad R, Al-Khader AA. Social and cultural issues in organ transplantation in Islamic countries. Ann Transplant. 2004; 9(2):11–13.

without trying to fit the patient into the strictures placed upon her through community leaders. Also, the clinician may be able to speak within a narrative so that the patient is not a foreign "other" and the clinician is not an outsider to be either completely deferred to or viewed with skepticism. In the case of oncofertility, the clinician may be able to assess whether oncofertility is the best form of reproductive intervention given the patient's sociological and psychological situation. Further, the clinician might be able to offer a slightly different narrative, such as that presented in Chapter 22 by Chaudhry in this volume, with which the patient might be more comfortable. Extensive conversations about the narratives within different religious, ethnic, economic, and other groups that move beyond simplistic juridical or theological positions will be required to truly determine whether oncofertility, regardless of its acceptability in academic discussions, is the right course of intervention for both patients who identify as Muslim and those who do not.

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# Chapter 22

# Unlikely Motherhood in the Qur'ān: Oncofertility as Devotion

**Ayesha S. Chaudhry**

## Introduction

As a new technology, oncofertility faces a whole host of ethical issues within and beyond the realm of religious studies. Within the framework of religious traditions, however, oncofertility faces unique challenges for each religious community. By considering the ethical implications of oncofertility in the context of particular religious communities, we might be able to discuss specific, tangible challenges in a fruitful manner. This chapter will discuss oncofertility in the context of Islamic conceptions of motherhood and Islamic legal discussions of sexuality, paternity, and the right to bear children. It will also provide a Qur'anic framework for Muslim women to think about their own choices when faced with the decision to utilize fertility interventions. The purpose of this chapter is to think through some of the competing narratives that a Muslim woman might consider as she makes her choices regarding oncofertility.

## Mohammad's Wives: Mothers of Believers

While it true that some Muslims have large families, motherhood is not an essential part of woman in Islamic theology and law. In fact, 'womanhood' in Islamic scholarship is not necessarily compromised by a woman's infertility. An example of this in Muslim history can be found in the model of Muhammad's wives. Many Muslim scholars, historically and in the contemporary period, considered Muhammad's wives to be exemplars for all Muslim women. In general, Muhammad is considered to be the ultimate exemplar for all believers, but scholars noted that his "maleness" prevented him from being a "perfect" example for women. While Muhammad could be an exemplar for women concerning their spirituality, moral character, and ethics, his example was necessarily limited concerning issues strictly

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pertaining to the female body. Here, scholars drew on the example of Muhammad's wives to fill the prophetic gap, by presenting them as the model for ideal wives, mothers, and sisters. These scholars based their arguments on a selection of verses in the Qur'an that threaten Muhammad's wives with double the punishment for their sins while also offering them double reward for their righteous deeds. These verses read,

> O Consorts of the Prophet! If any of you were guilty of evident unseemly conduct, the Punishment would be doubled to her, and that is easy for Allah. But any of you that is devout in the service of Allah and His Messenger, and works righteousness,- to her shall We grant her reward twice: and We have prepared for her a generous Sustenance (Q. 33:30–31).[1]

These scholars argue that the purpose of holding Muhammad's wives to a particularly stringent standard was that Muhammad's wives were meant to be emulated by other women. Thus, their sinful deeds would mislead many women, just as their righteous deeds would guide other women. Given the importance of Muhammad's wives as models for emulation, it is noteworthy that, with the exception of his first wife Khadijah, Muhammad did not have children with any of his other wives.

However, it is not enough merely look at the historical reality that Muhammad's wives did not bear children in order to understand Muslim ideals of womanhood. Despite the fact that lack of children did not compromise the womanhood of Muhammad's wives theologically and juridically, Muslims symbolically referred to them as the "Mothers of Believers." This symbolic title assigned to Muhammad's wives demonstrates the complex relationship between legal and theological Islamic discussions and the social mores of Muslim communities. By assigning the title of "Mothers of Believers" to Muhammad's wives despite the fact that most of them were not biological mothers, Muslims emphasized the social importance of motherhood in their understanding of womanhood. This disjoint between the biological and symbolic representation of Muhammad's wives highlights the tension often found between normative thought (Islamic law and theology) in Islam and Muslim practice. When studying normative Islamic sciences such as Islamic law one must always keep in mind that normative thought does not always translate into Muslim practice. In the case of oncofertility, whereas Islamic law might have an ambivalent attitude toward the new technology, Muslim attitudes might not be as ambivalent due to their particular social and cultural contexts where womanhood is defined by reproductive capacity.[2]

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[1] Abdullah Yusuf Ali. *The meaning of the Holy Qur'ān.* Beltsville, Md: Amana Publications; 1997: Q. 33:30–31.

[2] Serour GI. Bioethics in artificial reproduction in the Muslim world. Bioethics. 1993; 7(2–3): 207–17.

## Islamic Law on Sex, Paternity, and the Right to Bear Children

While Islamic law is not a necessary determinate of social mores and practice, it is nevertheless, a useful reference for normative discussion on fertility intervention technology. As with in vitro *fertilization* (IVF), Muslim jurists are mostly concerned with establishing paternity when it comes to technology such as oncofertility. As long as ownership of the ovarian tissue remains with the woman from whom it is removed, and any future eggs are impregnated with sperm from her husband, the legal problems surrounding the new technology are minimal.[3] If, on the other hand, the egg or sperm is donor, the juridical issues, surrounding IVF and oncofertility, become increasingly problematic due to the analogy to adultery and questions of paternity.[4] In Islamic law, establishing the patrilineal lineage of a child is paramount. For example, patriarchal concerns for paternity is the main reason that adoption is not permitted in Islamic law – a person can become the legal custodian and guardian of a child, but cannot make paternal claims on that child.[5]

Once paternity is established through the husband, however, Islamic law is generally ambivalent toward reproductive technologies. The ambivalence of Islamic law with technologies that enhance fertility is linked to its surprisingly lenient stance on issues related to the conception of womanhood and reproduction. For instance, although there are strict regulations in Islam regarding sexual partners – it is only permissible to engage in sexual relations with one's wives and/or concubines – procreation is not the sole purpose of sex in marriage. Sex for pleasure is perfectly acceptable and even meritorious. To this end, birth control is permitted in Islamic law, as long as it carries the consent of both spouses.[6] Similarly, although there are taboos against abortion in the Muslim world, jurists consider abortion to be a permissible act, in some schools up to 120 days into the pregnancy. The reason for this is theological rather than scientific and is based on a prophetic tradition (*ḥadīth*) wherein Muhammad was reported to have said that the spirit (*rūḥ*) of God is breathed into a fetus at 120 days. Until the spirit is breathed into a fetus, the fetus is not considered to have an independent claim on life and is merely an extension of the mother. As Abdulaziz Sachedina explains, the fetus "in utero" does not have

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[3] Abdulaziz Sachedina, Islam and biomedical ethics. Oxford: Oxford University Press; 2009:110. Even when jurists consider modern technology for purposes of fertility – such as IVF – to be "morally reprehensible," they concede that it is still a legally acceptable procedure, as long as the egg and sperm are from within the marital couple.

[4] Sachedina, Islam and biomedical ethics, p. 119. Donor eggs are less of a problem than donor sperm in Islamic jurisprudence, since the juridical concern is primarily the paternity of a child. Besides, polygamy is permitted in Islam, so the issue of the donor egg is less problematic than the donor sperm. For additional discussion on the issue of homogenic insemination, see Arbach O. Ethical considerations in Syria regarding reproduction techniques. Med Law. 2002; 21(2):395–401.

[5] For more on adoption in Islam, see Inhorn MC. "He won't be my son": Middle Eastern Muslim men's discourses of adoption and gamete donation. Med Anthropol Q. 2006; 20(1):94–120.

[6] Sachedina, Islam and biomedical ethics, p. 127

"independent and absolute inviolability."[7] However, once God's spirit enters the body – after 120 days – then abortion is prohibited unless it is undertaken to save the life of the mother.

The main question that technologies such as oncofertility raise in Islamic law is whether infertility is considered a "disability" or a "disease" – understood legally as "harm" – that would necessitate the use of oncofertility for treatment. This is an important question since the preservation of life is considered to be a central objective (*maqsad*) of Islamic law. If life is threatened, it is obligatory to preserve it by any means necessary. Although motherhood is considered sacred in Islam,[8] as demonstrated above, it is not considered an essential part of womanhood. The womanhood of Muhammad's wives was not compromised by their lack of biological offspring. Hence, it would be difficult to argue that infertility was considered to be either a "disability" or a "disease" which might in turn threaten life and thus make obligatory technologies such as IVF and oncofertility that enable women to bear children. Therefore, oncofertility would not be deemed a "necessity" for infertile women. Nevertheless, Islamic law considers offspring of men and women a basic marital right. For this reason, husbands and wives are permitted to divorce each other for infertility and impotence, respectively.[9]

Muslim women choosing to undergo oncofertility procedures would face few obstacles from Islamic law.[10] However, Muslim women might face hurdles from their communities, theologies, and their personal understanding of the role of God in their infertility. As Sachedina points out, Muslim women might feel that by choosing to engage in fertility-enhancing technology, they are demonstrating a lack of trust in God and that they are not "submitting" to His will in the matter of their infertility.[11] Submission to God, being the lexical meaning of "*Muslim*," is an important value for believers to embody. Hence, it would be a serious religious and personal obstacle if Muslim women felt that using technology such as oncofertility to preserve the possibility of having children – when God might have removed this possibility for them by the natural means of disease – meant that they were insufficiently submissive to God. To this end, I offer the model of three women in the Qur'ān – the divine scripture for Muslims – that may help Muslim women understand technology such as oncofertility as a "divinely sanctioned" intervention that might preserve their fertility.

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[7] Ibid., p. 126

[8] Ibid., 116

[9] Ibid., p. 108. While the right for husbands to divorce their wives for infertility is straightforward, wives must have already stipulated in their marriage contract that they can seek a divorce for impotence. In either case, infertility and impotence become legitimate causes for divorce.

[10] For more detailed discussion on Islamic law encouraging the use of assisted-reproduction technologies, see Serour GI. Islamic perspectives in human reproduction. Reprod Biomed Online. 2008; 17(Suppl 3):34–8.

[11] Sachedina, Islam and biomedical ethics, p. 114

## Unlikely Conception as Divine Intervention: Sarah, the Wife of Zakhariah, and Mary

The Qur’ān relates the story of three women who miraculously become pregnant through divine intervention. Pregnancy is a miracle in the case of two of these women because they are barren and in the case of the third because she is a virgin. The two barren women are Sarah, the wife of Abraham, and the unnamed wife of Zachariah. The virgin who miraculously becomes pregnant is Mary, the mother of Jesus.

In the case of Sarah, the Qur’ān narrates that angels appeared at Abraham’s home with “good” news. When they announced to Sarah that she would bear a son named Isaac, she responded with dismay and bewilderment, saying “Woe unto me! Will I bear a child when I am an old woman, and my husband here is an old man? That would indeed be a strange thing!”[12] The angels rebuked her saying, “Are you bewildered by God’s decree?” and ended by invoking God’s mercy and blessings on the house of Abraham.

In this Qur’ānic story, angels appear as messengers from God and speak to Sarah directly, who responds to them in her own voice. The interaction between Sarah and the angels is not mediated by Abraham. In the context of this story, the “good” news of a son is offered to Sarah, without her having asked for it. Sarah does not pray to God for a son, but rather a named son – Isaac – is offered to her, unprompted. Upon hearing news of a son, Sarah is not overcome with joy and gratitude. She does not treat this news as “good”. Rather she seems bewildered, dismayed, and worried about having a child in old age, when neither she nor her husband are young and capable of raising a child. When Sarah voices these concerns, treating the news as if it were a tragedy (“woe unto me!”), she is rebuked by the angels who emphasize God’s will in the decision for Sarah to have a son, reminding her that this is a blessing rather than a tragedy. Abraham’s reaction to the news of Isaac is not captured in this narrative.[13]

The second barren and elderly couple who receive a child miraculously from God are Zachariah and his wife. In this Qur’anic story, Zachariah – and not his wife – is center stage. According to this narrative, Zachariah is overwhelmed with anxiety about being alone and not having offspring, so he prays to God for a pure child. God fulfills Zachariah’s prayer, providing him with a son who will be a prophet. In one narration of this story, God responds to Zachariah’s prayer by saying, “So We responded to his prayer and We granted him Yahya: We cured/corrected his wife for

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[12] My translation of Q. 11:72. The entire story spans Q. 11:69–74. This story is intertwined with the story of Lot. The angels, in this narration, were on a mission charged by God to deliver both the good news to Abraham and Sarah of Isaac and also to destroy the people of Lot. The convergence of these two events in one story is worth exploring further but beyond the scope of this chapter.

[13] In the narration of this story, Abraham is actually more concerned about the fate of the people of Lot in this story.

him."[14] The news is delivered to Zachariah either through the voice of God Himself or through the voice of angels.[15] As with Isaac, Zachariah's son is also named by God; his name is Yahya, commonly known as John the Baptist. Although Zachariah had initially prayed to God for a son, acknowledging that he was elderly and infirm and his wife was barren, he is nevertheless amazed when he hears the news of a son. His amazement, unlike Sarah's, is joyous. God responds to Zachariah's amazement by emphasizing His role as "Creator," saying, "This is easy for Me – even as I created you when before you were nothing."[16]

The wife of Zachariah does not make an appearance in this story – all that is known of her is that she is barren. There is no discussion about how she might feel about giving birth at such an old age, or about raising a child with an elderly, infirm husband. In this story, God "corrected/fixed/cured" Zachariah's wife, presumably of barrenness, so that she could conceive a child for her husband. The patriarchal nature of this story is difficult to avoid – that barrenness in old age is treated as if it were unnatural and in need of curing/correction and that the barrenness of Zachariah's wife was 'corrected' for the sake of her husband without discussion of her personal desire and agency raises a number of questions. Still, this story offers a model for pursuing children despite natural impediments. While Sarah received a child without praying for one, Zachariah's wife must bear a child as a result of her husband's efforts in actively seeking a child from God. In these stories, having children, despite natural biological impediments such as old age and barrenness, is a miraculous and divine event.

The final story of a miraculous conception in the Qur'ān concerns Mary, mother of Jesus. This story might be especially relevant for young women considering oncofertility as an option, because in the Qur'anic story Mary is a young, unmarried woman who becomes pregnant by socially unacceptable means.[17] Throughout the Qur'ān, the most emphasized point about Mary is that though her pregnancy might be socially "illegitimate," her purity is not affected by her pregnancy. Rather, it only increases her in purity. Mary is referred to as the purest of women in the Qur'ān.[18] Another relevant aspect of the Qur'anic story of Mary is that Mary becomes pregnant by means of an angel that appears in human form.

Though this story is narrated in several parts of the Qur'ān, the basic story-line relates that Mary secluded herself away from her family. The text implies that this

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[14] My translation of Q, 21:90 with Yusuf Ali's translation. Abdullah Yusuf Ali. *The meaning of the Holy Qur'ān.*

[15] There are at least three versions of this story in the Qur'ān. See, Q. 3: 37–41, Q. 19:1–15, Q. 21:89–91

[16] This is my translation of Q. 19:9. See Abdullah Yusuf Ali. *The meaning of the Holy Qur'ān* for a variation of this translation.

[17] There are several stories about Mary in the Qur'ān. A couple of places where the story of her miraculous conception is discussed are Q. 3:42–59 and Q.19:16–35.

[18] Q. 3:42 reads "Behold! the angels said: "O Mary! Allah hath chosen thee and purified thee – chosen thee above the women of all nations." Abdullah Yusuf Ali. *The meaning of the Holy Qur'ān.* Q. 3:42.

seclusion was motivated by a spiritual quest. While Mary is in seclusion, God sends an angel to her in the form of a "well-proportioned" man.[19] It is not clear in the text how this man approaches Mary, but we can assume that he violates some social decorum, because she seeks refuge from him with God.[20] It is unlikely that she would have sought refuge from him unless she felt alarmed or threatened by his behavior. The angel reassures her that God sent him to her saying, "I am a messenger from your Lord, sent to give you the gift of a pure son."[21] Mary suspiciously asks "How will I have a son when no man has touched me and I am not an unchaste woman?"[22] The angel responds that this is the will of God and cites God as saying the same words He uses with Zachariah, "This is easy for Me." In this story, God further assures Mary that her conception of a son is a blessing from God (echoing the angel's words to Sarah) and that He intends to make her a "sign" for people. The story goes on to detail Mary's birthing experience, vividly capturing her anguished state. At one point, wishing that she had died rather than endure the pains of childbirth, Mary cries out "Woe unto me! Would that I had died before this and been a thing forgotten."[23] God does not abandon Mary in her childbirth, but provides her with a spring and a date tree to nourish her. When she is able to walk again, Mary returns to her people with a child in tow. Unsurprisingly, she faces the accusation of unchasteness from her community, who wonder how she could have conceived this "illegitimate" child when her parents were good people. In order to defend herself, Mary points to her baby, who then speaks to the people with claims of prophethood. Thus, Mary's miraculous conception and her speaking baby become a sign from God for the people.

In this story, divine intervention manifests itself in the form of an angel who appears to Mary as a well-proportioned man. This man becomes the means by which Mary conceives Jesus. Although an angel is an intermediary between God and Mary in her conception of Jesus, the birth of Jesus in the Qur'ān is compared to the creation of Adam. "The similitude of Jesus before Allah is as that of Adam; He created him from dust, then said to him: "Be" and he was."[24] Similarly, though Sarah and Zachariah's wife become pregnant by natural means within the institution of marriage, their conceiving of Isaac and John the Baptist is also attributed to the creative power of God. Further, becoming pregnant in unlikely circumstances did not compromise the chastity or submissiveness to God of any of the above-mentioned women. In fact, these women conceive children as a sign of their submission to God, who chooses them to conceive prophets. Sarah represents this submission most clearly because she is not overtly excited about bearing and raising a son at her age, yet is resigned to God's will. Mary also expresses her submission to God by bearing

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[19] Q. 19:17.

[20] Q. 19:18.

[21] Q. 19:19.

[22] Q. 19:20.

[23] Q. 19:23.

[24] Abdullah Yusuf Ali. *The meaning of the Holy Qur'ān*, Q. 3:59.

a son despite the social censure she is likely to face as a result of giving birth out of wedlock. Thus, the "unnatural" and miraculous conception by Sarah, the wife of Zachariah, and Mary represent a model for contemporary Muslim women who hope to preserve their fertility and conceive through "unnatural" means involving human intervention. Human and angelic mediation in these stories do not diminish the creative power of God, but rather reaffirm it.

## Conclusion

What might be called the "Islamic" approach to motherhood, fertility and sexuality is complex, nuanced, and sometimes contradictory. Motherhood is not an essential part of womanhood, but it is nevertheless a sacred duty that is closely connected to God's creative power. While most of Muhammad's wives offer a model of womanhood that is not fixed to biological motherhood, their status is nevertheless intertwined with the symbolic power of motherhood. They are the "Mothers of the Believers," yet most did not have children. Juridically, the purpose of sex in marriage is not solely procreation, and birth control and abortion are permissible. However, the right to have children is a basic spousal right, and infertility and impotence form legitimate grounds for divorce. When there is infertility or impotence, Muslim jurists are open to technological advances that enhance women's ability to bear children so long as paternity is safeguarded. While there is often pressure to procreate in Muslim communities, Muslims also stress the importance of being content with God's will in the matter of one's (in)fertility.

Given the centrality of submitting to God's will, pursuing "unnatural," human efforts to enhance fertility might be seen as subverting God's will rather than submitting to it. The stories of Sarah, the wife of Zachariah, and Mary are incidents of divinely sanctioned unnatural conceptions narrated in a patriarchal context, which raise as many questions as they answer. Why is barrenness in old age – a natural phenomenon – something that needs to be corrected, fixed, or cured? Why is women's agency in bearing children secondary to the desires of their husbands, lineage, or divine decree? Still, these stories offer new ways for women to think about their choices when making a decision about their own fertility. If barrenness is natural and therefore representative of God's will, seeking and conceiving a child despite such "natural" barriers can also be indicative of God's will. Given the variegated contexts of Muslim women facing the choice of using oncofertility, Muslim women will relate to the examples of Muhammad's wives, Sarah, the wife of Zachariah, and Mary in different ways. They might relate more or less to one model or another or not relate to any of them at all. Nevertheless, these Qur'anic stories offer a religious framework for women to think about understanding their choices for fertility as harmonious with rather than subversive of Divine Will.

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# Chapter 23
# Technology and Wholeness: Oncofertility and Catholic Tradition

**Paul Lauritzen**

## Introduction

The remarkable scientific work on fertility preservation that is documented in the early chapters of this volume will inevitably give rise to moral and religious questions about the use of technology to reproduce. In this regard, oncofertility is no different from other forms of assisted reproduction that have led to extensive debate among ethicists and moral theologians. In the case of many forms of reproductive technology, the ethical debate *followed* rather than *preceded* the widespread adoption of new techniques in a clinical context. It is thus both notable and commendable that the oncofertility research community seeks to explore the broad implications of oncofertility techniques before they are used widely among cancer patients.

The goal of this chapter is to examine oncofertility from the perspective of Catholic moral teaching on assisted reproduction. To facilitate this examination, the chapter focuses narrowly on one particular avenue of oncofertility research, namely ovarian tissue cryopreservation [1]. Although the Catholic church has not issued a specific directive about this technology, the general teaching on assisted reproduction is sufficiently clear that we can reasonably extrapolate from prior teaching to predict the likely response of the Vatican to this technology [2, 3]. At the same time, ovarian tissue transplantation may lead us to rethink Catholic teaching in interesting ways. In part one of this chapter, I review Catholic teaching on assisted reproduction with an eye to anticipating Catholic teaching on oncofertility. In part two, I address the question of whether new techniques in oncofertility might lead us to rethink Catholic teaching.

## Part One

We begin by noting that ovarian tissue cryopreservation and transplantation can take a number of different forms. As diagram 1 indicates, ovarian tissue research

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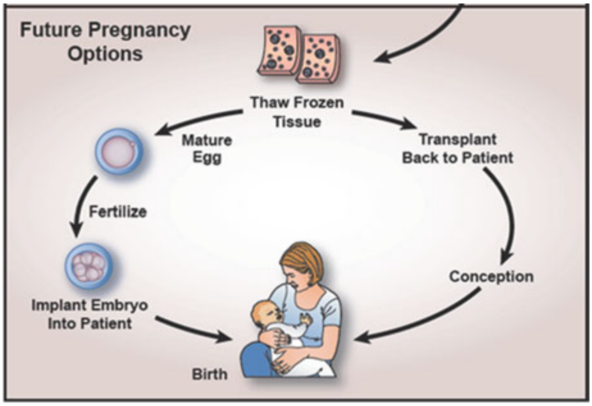

**Diagram 1**

follows two main paths. Assuming that ovarian tissue has been surgically removed and frozen prior to the onset of cancer treatment, a woman who has survived cancer and desires children can take either path. Either she can have her ovarian tissue thawed to seek in vitro maturation of follicles to produce mature eggs prior to an IVF attempt or she can pursue an autologous tissue transplantation of her thawed ovarian tissue back into her own body with the hope of restoring endocrine and ovarian function prior to “natural” conception. What will the Catholic church say about these two paths of ovarian tissue transplantation?

To answer this question, we must turn to two documents that have set out Catholic teaching on reproductive technology, *Donum Vitae* – issued in 1987 – and *Dignitas Personae* – issued in 2008. Released by the Congregation for the Doctrine of the Faith (CDF) shortly after the dawn of the modern era of assisted reproduction and when Pope Benedict, then Cardinal Ratzinger, was prefect of the CDF, the document is impressive. Unlike many other groups at the time, the congregation recognized the significance of the technology of in vitro fertilization, and *Donum Vitae* systematically examined the implications of a technology that allows scientists to manipulate gametes and embryos in the laboratory. Indeed, most of the major moral issues that have arisen in the wake of this technology were anticipated and addressed by the congregation in the *Instruction*. Freezing embryos, experimenting on them, selling gametes, and gestational “services,” turning procreation into a kind of manufacturing process – all were taken up in *Donum Vitae*.

According to the *Instruction*, there are two fundamental values that should govern moral reflection on assisted reproduction: (1) “the life of the human being called into existence and (2) the special nature of the transmission of human life in marriage” [2]. The first value, namely the right to life of the embryo from conception, effectively prohibits any form of assisted reproduction that fails to accord embryos complete moral respect as persons. In vitro fertilization, non-therapeutic embryo experimentation, freezing embryos, and gestating embryos in non-human hosts or paid human hosts all fail to honor the value of a human life called into existence through assisted reproduction. In short, this value served to shape judgments about what could be done with human embryos.

By contrast, the appeal to the value of the special nature of the transmission of human life in marriage functioned differently. Whereas respect for embryonic life primarily constrained technologies that involved creating or manipulating embryos in the laboratory, the commitment to keeping sex and procreation together within a marriage responded to reproductive medicine's new abilities to disembody procreation by facilitating reproduction through the isolation and manipulation of sperm and egg in a laboratory. The opposition to procreation that was not the result of a loving act of sexual intercourse effectively functioned as a barrier to the tendency within reproductive medicine to reduce the creation of human life to the mere manipulation of gametes.

If these are the fundamental values that the Catholic church will use to assess ovarian tissue cryopreservation, what is Church teaching likely to be? The answer can be represented in relation to diagram 2. Here, we see that there is a divide between the two avenues of research pursued in relation to ovarian tissue preservation. The research represented by the left side of diagram 2, namely that designed to facilitate the in vitro fertilization of human eggs followed by embryo

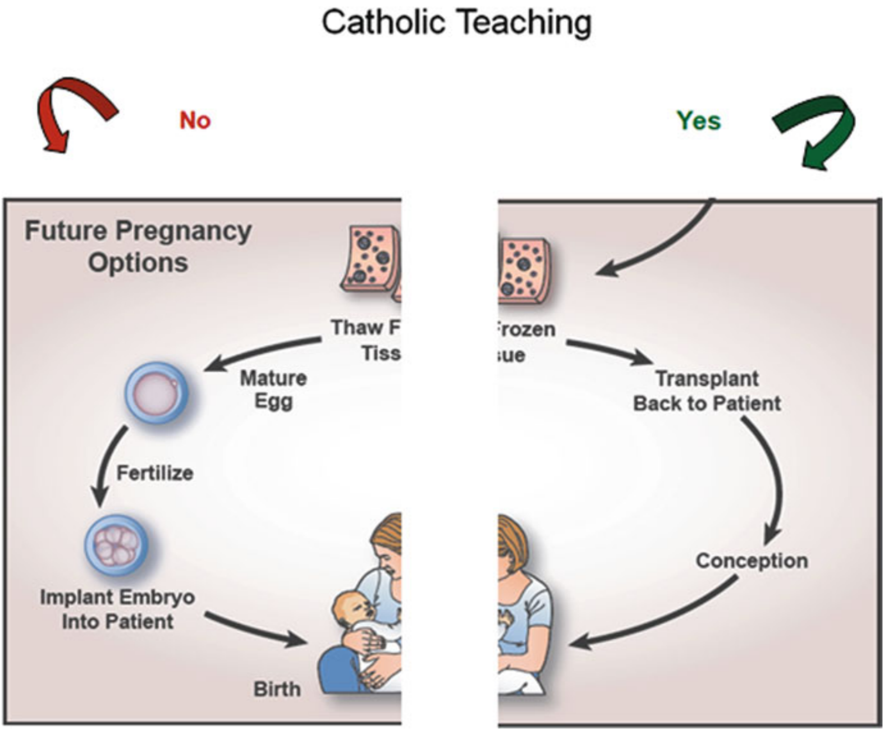

Diagram 2

transfer is almost certain to be rejected by the Vatican. Given the fundamental values set out in *Donum Vitae*, it is hard to see how the Vatican can do anything other than reject this line of research. Ovarian tissue preservation for the purpose of maturing and fertilizing human eggs in the laboratory violates both values. The life of the human being created in the laboratory is not respected by this technology and human procreation is separated from sexual intercourse and thereby disembodied.

By contrast, research directed toward the right side of diagram 2, specifically research that involves orthotopic ovarian tissue transplantation, appears to be unproblematic, if judged by the twin values of *Donum Vitae*. In relation to the two values of respecting the dignity of the human embryo as a person with rights and respecting the inseparable connection between sex and procreation, this technique appears untroubling, for neither of these values is necessarily threatened by this new technique. Orthotopic reimplantation of ovarian tissue does not involve creating embryos in the laboratory and if the transplant is successful procreation will follow from marital intercourse. Thus, orthotopic grafting of ovarian tissue should be acceptable given current Church teaching.

Indeed, the technique seems profoundly consonant with the view of human nature set out at the start of *Donum Vitae*. Quoting Pope John Paul II the document reads "Each human person, in his absolutely unique singularity, is constituted not only by his spirit, but by his body as well. Thus, in the body and through the body, one touches the person himself in his concrete reality. To respect the dignity of man consequently amounts to safeguarding this identity of the man *'corpore et anima unus'*, as the Second Vatican Council says (*Gaudium et Spes*, 14, par. 1)." I do not think it much of a stretch to say that the effort to help a cancer survivor to have children after the fertility-ending effects of cancer treatment is partly an attempt to stitch back together a spiritual and bodily unity that cancer may have sundered. Nor is it a stretch to say that ovarian tissue transplantation and the return to reproductive function that it may facilitate profoundly touches the body and thus the person whose sense of bodily integrity and spiritual wholeness was deeply threatened by cancer.

Given that orthotopic tissue transplants are experimental, they should not currently be offered to cancer patients as standard clinical practice. Indeed, given that freezing and thawing of ovarian tissue is itself still experimental, the option of storing ovarian tissue should only be offered to patients as part of an experimental protocol that has been approved by an ethics committee. But if freezing ovarian tissue is offered as part of a research effort, I see no moral reason why a Catholic patient should not enroll in such a study. Similarly, if a woman has stored ovarian tissue, there seems to be nothing intrinsically wrong with participating in a research study that involves placing this tissue back in her body in the hopes of conceiving a child naturally. We will want to be as sure as we can be that conceiving a child after storing ovarian tissue does not result in significant risk of harm to the resulting child. But conceiving a child in this fashion does not seem *per se* wrong, and Catholic tradition ought to embrace such a treatment when it is no longer experimental.

If we turn from *Donum Vitae* to the most recent *Instruction* issued by the Vatican, *Dignitas Personae,* these conclusions are confirmed. In the fall of 2008, the Congregation for the Doctrine of the Faith updated the teaching of *Donum Vitae.* The congregation reviewed its previous conclusions about reproductive technologies and addressed new technologies that have emerged during the 20 years since *Donum Vitae* was issued. The document effectively reaffirms the conclusions set out in *Donum Vitae,* but it is worth looking at this newer *Instruction* nevertheless.

One notable feature of the *Instruction* is that it begins by highlighting the Vatican's commitment to science and its hope that Christians will continue to dedicate themselves to scientific inquiry. The Church, the document reads, "seeks to offer a word of support and encouragement for the perspective on culture which considers science an invaluable service to the integral good of the life and dignity of every human being" [3]. At the same time, the Congregation for the Doctrine of the Faith again insists "the ethical value of biomedical science is gauged in reference to both the unconditional respect owed to every human being at the moment of his or her existence and the defense of the specific character of the personal act which transmits life" [3]. Thus, the two fundamental values set out in *Donum Vitae* are reaffirmed here.

However, *Dignitas Personae* articulates a slightly different formulation of the values that infertility treatment must respect. "With regard to the treatment of infertility," the CDF writes, "new medical techniques must respect three fundamental goods" [3]. These goods are (1) the right to life of a human being from conception to natural death; (2) the unity of marriage, which requires that spouses reproduce only with each other; and (3) the integrity of human sexuality, which requires that conception take place through sexual intercourse. Moreover, in giving examples of how infertility treatment may respect these goods, *Dignitas Personae,* provides further clarity about the likely position the Church will take on ovarian tissue transplantation. Infertility treatment is not to be rejected per se. For example, hormonal treatments for infertility and surgery for endometriosis are both perfectly acceptable. In the language of the *Instruction,* these techniques are "authentic" because "once the problem causing the infertility has been resolved, the married couple is able to engage in conjugal acts resulting in procreation, without the physician's action directly interfering in that act itself" [3].

If this is the standard by which to evaluate infertility treatment, then clearly some of the current work in oncofertility will be acceptable in terms of Catholic teaching and some will not. Research on ovarian tissue cryopreservation for the purpose of maturing eggs in the laboratory prior to fertilization in vitro will be morally unacceptable in Catholic teaching. By contrast, ovarian tissue cryopreservation for the purpose of autologous transplantation should be acceptable.

## Part Two

While it is worthwhile to reflect on oncofertility in light of Catholic teaching on reproductive technology, is it also useful to review Catholic teaching in light of oncofertility? If I am right that the Vatican should embrace ovarian tissue transplants, it will be because Catholic teaching on assisted reproduction is primarily concerned with respecting embryonic life and with avoiding the reduction of procreation to the manipulation of gametes, as if human procreation is a manufacturing process. As we have seen, Catholic opposition to certain forms of assisted reproduction is not rooted in an anti-technological mindset, but rather in a concern that technology not dominates an area of human life that should be rooted in love and a commitment to the welfare of children. This is at least partly why the CDF insists that procreation should come from a loving act of sexual intercourse.

If the technique of orthotopic ovarian tissue transplantation lives up to its promise, it will allow women facing fertility threatening cancer treatment to store ovarian tissue in the hope of having a family down the road through means that would not violate the two fundamental values set out in *Donum Vitae*. Yet it is also important to note that ovarian tissue transplantation can be done in a number of different ways and that the technique itself may lead us to rethink how we have approached fertility treatment in the past. To see this, consider the work of Sherman Silber and his colleagues reported in the *New England Journal of Medicine* a few years ago [4]. It involved identical twins, one of whom suffered from ovarian failure at age 14. When the twins were in their mid-twenties, the sister who remained fertile donated ovarian cortical tissue to her twin for surgical transplantation. After several months, the infertile twin began to ovulate again and went on to conceive a child "naturally" with her husband.

This case points to a conundrum posed by modern biotechnology: new technology frequently confounds our traditional categories of thought. For example, in this instance we might ask whether the child conceived is the offspring of the infertile twin. The infertile twin has produced a mature egg in vivo, conceived an embryo through intercourse with her husband, and sustained a pregnancy that resulted in the birth of a child who, in the traditional language, was begotten not made. Nevertheless, the tissue containing the immature eggs came from another woman, namely her sister. The case is complicated by the fact that the twins are identical. Thus, it might not even be possible to determine whether the child was the genetic offspring of the fertile twin. Catholic teaching on assisted reproduction has insisted that genetic and social parenthood not be separated. But what does genetic parenthood mean in the context of an ovarian tissue transplant between identical twins? Should an ovarian tissue transplant be treated more like, say, a kidney transplant than like egg donation? After all, like organ transplants ovarian tissue transplantation restores a complex biological system to normal function.

If we return to the passage from *Dignitas Personae* quoted above, it is not clear why the Catholic church would condemn ovarian tissue transplants between identical twins. Recall that the criterion for an "authentic" reproductive intervention is that "the married couple is able to engage in conjugal acts resulting in procreation, without the physician's action directly interfering in the act itself." Yet, that is precisely the result of the ovarian tissue transplantation in this case; the recipient twin begins to ovulate again and she is able to conceive a child with her husband through sexual intercourse.

The fact that the ovarian tissue comes from the identical twin may divert our attention from the reality that genetic and social parenthood are separated by this procedure, but we need to address that reality to explore fully how this technology may lead us to reassess the foundations of Catholic teaching on reproductive technology. Because the donor and the recipient essentially share a genome, it may not be clear that an ovarian tissue transplant is a form of egg donation. Suppose we vary the case. Instead of an ovarian tissue transplant from one sister to her identical twin, let us imagine a case in which ovarian tissue is transplanted from a living, non-related donor to a woman suffering from ovarian failure. Let us further imagine that the transplant is successful; the recipient begins ovulating and conceives a child through sexual intercourse with her husband. The child will be the genetic offspring of the donor and the recipient's husband, even though the child was conceived through an act of sexual intercourse between husband and wife, which involved no direct intervention by a physician.

This case poses a significant challenge to Catholic thought. If we review this case in terms of the two fundamental values set out in *Donum Vitae,* non-autologous ovarian tissue transplant appears to be morally acceptable. Such a procedure does not involve manipulation or destruction of human embryos, and the child that results from this procedure is conceived through a loving act of sexual intercourse of a married couple. Even the third value set out in *Dignitas Personae*, namely "the right within marriage to become a father or mother only together with the other spouse," is not obviously violated with this procedure.

Yet, Catholic teaching clearly rejects the so-called heterologous procreation. Here is how *Donum Vitae* defines heterologous procreation:

> By the term *heterologous artificial fertilization or procreation*, the *Instruction* means techniques used to obtain a human conception artificially by the use of gametes coming from at least one donor other than the spouses who are joined in marriage. Such techniques can be of two types
>
> a) *Heterologous IVF and ET*: the technique used to obtain a human conception through the meeting in vitro of gametes taken from at least one donor other than the two spouses joined in marriage.
> b) *Heterologous artificial insemination*: the technique used to obtain a human conception through the transfer into the genital tracts of the woman of the sperm previously collected from a donor other than the husband [2].

We can now state the problem more directly. The Catholic church has framed its teaching on reproductive technology as if procreation that results in the birth of a child who is not the genetic offspring of one of the spouses in a marriage was conceived either by artificial method or by sexual intercourse with someone who is not one's spouse. Non-autologous tissue transplantation followed by natural conception demonstrates that this framework is mistaken and must be revised. In effect, this new technology forces the question: What precisely is the foundation of Catholic opposition to "heterologous" procreation? Is this opposition rooted in the tradition's non-dualistic view of the body and a natural law understanding of the necessary integration of sex, marriage, and procreation or is it rooted in a theological understanding of marriage that requires maintaining the connection between genetic and social parenthood?

The most responsible response to this question is that the answer is just not clear. At almost every point at which *Donum Vitae* and *Dignitas Personae* discuss heterologous procreation these two distinct approaches are collapsed into one another, often in the same sentence. Yet, if we examine these different strands of argument separately in relation to non-autologous ovarian tissue transplantation, we may reach different conclusions.

Consider, first, the approach rooted in a theological understanding of human embodiment and a natural law approach to human sexuality. We have already noted a passage from *Donum Vitae* that succinctly captures Catholic teaching that the human person is a union of body and spirit. Man cannot be reduced to his body; neither can he be treated as pure spirit. And this is part of the problem with artificial procreation: it treats procreation as if it is merely a kind of mechanical production, as if humans are not a unified whole. In disembodying procreation, reproductive technology makes the mistake of reducing the body to instrumental status.

This account of human embodiment dovetails with natural law teaching on the necessity of maintaining the integrated structure of sex, marriage, and procreation. This teaching is the basis of the Church's insistence that procreation must result from sexual intercourse. Sex is designed to be both unitive and procreative; to separate these dimensions of sexuality is to violate the natural order. With regard to preventing conception, this reasoning leads to a prohibition on the use of artificial contraception. With regard to infertility, this reasoning leads to a prohibition on interventions that bypass sexual intercourse.

We have seen, however, that even non-autologous ovarian tissue transplantation does not appear to violate these norms. Assuming that the transplant restores endocrine and ovarian function, conception will be the result of a loving bodily act of sexual intercourse between husband and wife. Procreation is not disembodied through this technique; on the contrary, ovarian tissue transplantation arguably restores a sense of bodily and spiritual integrity to a woman whose sense of wholeness may have been shattered by cancer.

What if we evaluate non-autologous ovarian tissue transplantation in terms of Church teaching on the vocation of marriage? Here the answer is less clear. Once again, we must turn to a passage in *Donum Vitae* for guidance. The passage is long, but worth quoting in full.

> Recourse to the gametes of a third person, in order to have sperm or ovum available, constitutes a violation of the reciprocal commitment of the spouses and a grave lack in regard to that essential property of marriage which is its unity. Heterologous artificial fertilization violates the rights of the child; it deprives him of his filial relationship with his parental origins and can hinder the maturing of his personal identity. Furthermore, it offends the common vocation of the spouses who are called to fatherhood and motherhood: it objectively deprives conjugal fruitfulness of its unity and integrity; it brings about and manifests a rupture between genetic parenthood, gestational parenthood and responsibility for upbringing. Such damage to the personal relationships within the family has repercussions on civil society: what threatens the unity and stability of the family is a source of dissension, disorder and injustice in the whole of social life [2].

Given this passage, it seems likely that the Vatican will reject non-autologous ovarian tissue transplantation. Before we draw that conclusion, however, it is important to review this passage in light of our previous concerns about the failure to distinguish two distinct lines of argument about heterologous procreation. Let us review this passage a bit more closely to see exactly what claims are being made. We can distinguish at least four claims here.

(1) *Recourse to the gametes of a third person, in order to have sperm or ovum available, constitutes a violation of the reciprocal commitment of the spouses and a grave lack in regard to that essential property of marriage which is its unity.* In the absence of a procedure like non-autologous ovarian transplantation, this statement would appear to be relatively straightforward because using the gametes of a third person meant that the conception did not result from a loving act of sexual intercourse between spouses. Yet, given the possibility of ovarian tissue transplants, we must now ask whether the language of having "sperm and ovum available" is not really a concern about procreating without sexual intercourse. Similarly, the concern about "unity" may represent a rejection of the possibility of an infertile spouse having sexual intercourse with a donor.

(2) *Heterologous artificial fertilization violates the rights of the child; it deprives him of his filial relationship with his parental origins and can hinder the maturing of his personal identity.* This section of the passage suggests something new. The opposition to heterologous procreation is not here based on issues of disembodiment. Rather, the concern appears to be tied to genetic connection between parents and children. Although the formulation of the argument has a utilitarian cast, the basis for the argument is genetic connection. We will return to this below.

(3) *Furthermore, it offends the common vocation of the spouses who are called to fatherhood and motherhood: it objectively deprives conjugal fruitfulness of its unity and integrity.* Once again, the claim appears to be rooted in a natural law concerns about the structure of human sexuality, a structure that, as we have seen, ovarian tissue transplantation does not violate.

(4) *It brings about and manifests a rupture between genetic parenthood, gestational parenthood, and responsibility for upbringing.* Like claim (2), the issue here is explicitly genetic connection. This is something new and different from the other claims embedded in *Donum Vitae*.

I believe the positions articulated in items (2) and (4) suggest that Catholic teaching will be opposed to non-autologous ovarian tissue transplantation. The question is whether there are good reasons for accepting (2) and (4) independent of concerns about embodiment and the unitive and procreative dimension of embodied sexual love. This is a question we have not asked before. It is a pressing question because the temptation will be to answer it by relying on a kind of genetic essentialism that Catholic tradition would repudiate in other contexts.

William Werpehowski has argued that accepting the importance of a genetic connection between a married couple and their children need not rest on genetic essentialism [5]. He cites Leon Kass's argument that one can want one's "own" children without giving genetic connection a moral valuation that it does not deserve. According to Kass, when couples say they want a child of their own, they often use traditional expressions like "my seed," "flesh of my flesh," and "sprung from my loins," and these expressions actually express the desire "to embody, out of the conjugal union of their separate bodies, a child who is flesh of their separate flesh made one." In addition, says Kass, in seeking conjugal fruitfulness, a couple seeks "a new branch of their joined family tree."

Once again, however, non-autologous ovarian tissue transplantation forces us to ask, why a child conceived naturally and carried in the womb of a woman who gives birth to the child is not a child who is flesh of a couple's flesh made one. I believe that a child so conceived is flesh of the couple's flesh, and so appealing to this idea to reject non-autologous ovarian transplants is not plausible. The idea of establishing a "new branch of their joined family tree" is more promising, but to evaluate this line of argument requires exploring conceptions of parenthood and the significance of genetic relation to parenthood, outside of the framework of natural law that emphasizes conjugal fruitfulness in family life.

The philosophical literature on parenthood is a useful resource here, but that literature suggests that a genetic conception of parenthood has serious problems [6–11]. Consider, for example, the work of Tim Bayne and Avery Kolers. In a series of articles on the topic, they have argued for a "pluralist" conception of parenthood and against a genetic definition of parenthood [6–8]. Bayne and Kolers acknowledge that a genetic conception of parenthood is intuitively plausible, for many people see parenthood as rounded "in the natural derivation of one person's genetic constitution from the genetic constitution of others" [6, p. 273]. Nevertheless, two points should be established right away.

First, it is important to emphasize that a genetic conception of parenthood rests on the derivation of genetic relations and not genetic connection itself. Obviously, a person has a closer genetic connection to his or her identical twin than to a genetic offspring, but this does not make the person a parent to his or her sibling. Second, it is important to distinguish biological connection and genetic connection. These are not the same, but treating them as if they are may contribute to the initial plausibility of a genetic view of parenthood.

To see the significance of this second point, it may be useful to explore why we equate biological and genetic connection. The answer, I believe, is that we have become so enthralled by genetic technology that it has become the lens through which we see all biological phenomena. Barbara Katz Rothman has captured this well when she writes: "The solidity of the body is breaking down as we imagine activity at the cellular level. The wholeness of the self is fragmenting as we think about lists of instructions, the pages and pages of ATCGs that make up each of us" [12, p. 40].

Even if we do not insist on recognizing the wholeness or solidity of the body, there is no denying its materiality, and focusing on material contribution makes a difference. Suppose, for example, that motherhood is defined less in terms of genetic contribution and more in terms of material contribution. Seen from this perspective, a woman who conceives a child after a non-autologous ovarian tissue transplant is unquestionably the mother of the child, for while the child's genetic material is not derived from hers, the genetic material is a negligible part of the child's material constitution [12, p. 276]. By contrast, her material contribution to the child's constitution is enormous.

## Conclusion

The Catechism of the Catholic church defines the nature of the family this way: "The conjugal community is established upon the consent of the spouses. Marriage and the family are ordered to the good of the spouses and to the procreation and education of children" [13, Section 2201]. Because marriage and the family are central in Catholic teaching and because marriage is ordered to procreation, the Catholic church strongly endorses scientific efforts to treat infertility. At the same time, Catholic teaching is concerned to safeguard respect for human life, including early embryonic life, and it insists on the special nature of transmitting human life through sexual intercourse.

Given these tenets of Catholic teaching, the Vatican will be open to the work being done in the emerging field of oncofertility. At the same time, certain techniques of oncofertility will be unacceptable. In vitro maturation of eggs followed by fertilization in vitro will not be acceptable. By contrast, autologous ovarian tissue transplant is likely to be accepted by the Church. Given the teaching set out in *Donum Vitae and Dignitas Personae,* it also seems unlikely that the Vatican will accept non-autologous ovarian tissue transplantation. Yet, as I have tried to show in this chapter, non-autologous transplants pose an interesting question for Catholic teaching.

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# Chapter 24
# Jewish Perspectives on Oncofertility: The Complexities of Tradition

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## Introduction

I begin this reflection on Jewish bioethical response to the dilemmas within oncofertility with a familiar caveat: there is no one particular authority on Jewish ethics, nor even on the legal, or halachic norms that govern Jewish community practice. Jewish bioethics has historically been an account of optimism about research, as a project of repair in a broken or unfinished world [1]. While Freedman has raised some cautionary caveats about the need for full consent and safety [2] and while others have raised some questions of justice (including this author), the main thrust of Jewish responses to both artificial reproduction and to new technology in treating cancer has been to celebrate the advances as a part of the general goal of human development, creativity, and capacity. Unlike Catholic moral theology, the moral status of the human embryo is not that of a person, or even a potential person. The embryo created in a Petri dish is an artifact, existing extracorporeally, and having no potential of being other than what it is, unless complex science, a women's hospitality, and a great deal of luck combine to allow a pregnancy to develop. Halachah, or Jewish law, is clear about both the duty to learn [3] and the duty to heal [4] and clear about essential commitments to a pronatalist position on creating embryos. All of this has driven both a robust support for research in medicine and a practical enthusiasm for public funding for research and its emerging therapies. International Hadassah, the Jewish Women's Organization, diasporic Rabbinic boards, and congregational organizations, as well as Israeli state policy clearly support research on embryos, stem cells, genetics genomic and made robust social and economic support of ART a matter of urgent policy. Thus oncofertility, a technology which builds on the fields of ART to treat cancer sequella, seems poised to be normatively supported by Jewish text and tradition.

Oncofertility in Jewish thought is framed by several constraints. A Jewish contribution to the debate on fertility and infertility is based both on what is written

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and what is preformed. Normative Jewish practice is based on textualized reasoning: an analysis of the problems of a tangible sensory and social world. Hence, both the concerns of historical context and the rigor of traditional canonical texts create social policy. When new historical situations arise, and the daily enactment of community and faithfulness shifts against political, scientific, or physical contingencies, a process of heightened discourse reshapes the new enactments. In critical ways, the questions of the environment, of population, are in constant flux. For Jews, the cultural and economic realities of modernity affect religious practice, social justice, and ethical norms. Family life, families, childrearing, and sexuality are part of the practice of religion. In reflecting on Jewish ethics, one considers the whole of human activity and the whole of the community as well: women as well as men are moral agents, the lifeworld of the family, of women and of children, are central concerns of religion. This discourse is primarily contained in the extensive debate and exegesis of the rabbinic literature, which is primarily although not exclusively collected in a set of volumes called the Talmud. It is a record of an oral discourse, in which contention and casuistic narrative ethics both determine and discuss the Hebrew Scriptures and struggle to apply them to daily life. In an elaborate linguistically complex oral debate, later codified in the written Talmud, the teachers of the period described 613 commanded acts named as "the mitzvot" (200 BCE–500 CE). Both the study of this linguistic world and the ongoing efforts to shape and be shaped by the practice of the commandments defined the moral universe of observant Jews in the centuries since this time.

Jewish law developed in the 1,500 years since the redaction of the Talmud by an ongoing series of "responsa" to questions about the legal code discussed in the Talmud. Difficult cases of social crises of all types are brought before decisors and scholars who rule on the facts of the cases, on the methodological principles of logical discourse, and on certain key principles of relationships in the familial, ritual, civic, and commercial spheres. Each commentator is in discourse with those who came previously and yet is confronted by changes in context: political and cultural shifts as well as scientific understandings that could not have been available to previous generations. This process of query and response continues into the present. Nowhere is this more publicly evident than in the rapidly changing field of reproductive health.

The drama of the Biblical texts, it could be argued, is the problem of infertility. Far more attention is given to infertile women (note that women were historically seen as the source of infertility) than to war or conquest in the first five books of the Hebrew Scripture that are the Torah. The promise that is the basis of the covenant itself is the repeated assurance that the tribe of Abraham will be continued, made numerous, and that the Jewish future and through it, the human future is safe. The key text on the issue of family planning arises in Yevamot,[1] one of six tractates

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[1] Yevamot means "sisters in law" or levirate wives.

or sections of the Mishnah.[2] In this passage, the rabbis begin by discussing the problem of how to continue the line of a man who has died childless. While his wife can remarry, his line will end, and the concern of the Biblical text was to enact a system to avoid this. Hence, the idea that his closest biological kinsman will marry his widow, and she will claim the children born as her dead husband's, entitled to his inheritance. The Mishnaihic text deepens the question about the nature and meaning of the obligation to have children:

> A man may not desist from (the attempt to) procreate unless he already has children. Bet Shammai says, two sons, but Bet Hillel says, one son and a daughter, for it says "male and female He created them." [5]. If he took a wife and remained with her for 10 years and she did not give birth, he is not allowed to desist (from the attempt to have children). If he divorced her, she is permitted to marry someone else. And the second husband is allowed to remain with her for 10 years... A man is commanded to procreate but not a woman. R. Yohanan b. Baroka (disagrees and) says: About both of them it says "And God blessed them and said to them be fruitful and multiply.

What is occurring here? The biblical text sets the standard for the halachic requirement that a person must have children. There is debate among the sages of the Mishnah about whether a girl child will "count." After these children are born, the text implies the duty to have sexual relations with his wife, clearly required in other places, may continue without procreative intent, which implies further that birth control can be used. (In texts of the Mishnah, there is reference to both women and men drinking a "sterilizing potion" to achieve this.) Some commentators add that it means that a man may, after he has had two children, and his wife has died, or he has divorced, marry a woman who cannot have children or that he may even stay single.[3] The text continues with a concern about infertility. The implication here is that both women and men desire children, and hence, after a childless marriage, they both are permitted to marry someone else. The text ends with an argument about the obligations that women hold toward childbearing, and the argument stands.

The Gemora, the subsequent generational commentary on the Mishneh, continues where we left off. In the Gemora, the rabbis debate whether the command to "replenish and subdue the earth" is addressed to both women and men. Typically, there is a debate, first about gender and nature: Rabbi Ile'a declaring that it is not "the nature of women to subdue."[4] After more debate, a consensus emerges. Women are not *required* to procreate. Then three critical cases are brought into the debate, stories that will allow for two centuries of discourse. In the first, a woman who is childless comes to ask for a divorce so she can marry and have children in another

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[2] The Mishnah is the first level of textual commentary on the text of the Bible and interpretive laws derived therein. The word means "to study." With the Gemora, a later commentary on the Mishnah, it makes up the Talmud, a record of oral debates that spans five centuries, containing narrative, exegesis, and legal opinions on public policy and faith rituals.

[3] Hauptman, Judith, Rereading the Rabbis (p. 131).

[4] "And then, about grammar: 'subduing' requires two. 'Thou' means two – so it must apply to both men and women!"

marriage.[5] There is debate: if a woman is obliged to create then she must be given a divorce – but is she obligated? Or is it a matter of choice? Another story is told, in which a woman comes with a similar plea, her desperation evident in the text "What will become of a woman like myself in old age! (without children)... Does not a woman like myself require a staff in her hand and a hoe for digging a grave!" It is a compelling plea: the rabbis decline her request at first, but when they consider her argument, they accept it and they allow her divorce – a woman may make her own decisions and take on this obligation to bear children. But then a third case is told: If procreation is a woman's choice, may a woman decide to refrain from childbearing, *even if her husband wants more children?* Here, the textual account continues: Judith, the wife of Rabbi Hiyyah, endures an odd and painful twin pregnancy. As soon as she can, she disguises herself and comes to the house of study, where her husband is deciding cases of law. She asks about the halachic texts that define the obligation for procreation as having two children and queries whether one must continue childbearing once that has been fulfilled.

> "Is a woman commanded to propagate the race?"–"No," he replied. And relying on this decision, she drank a sterilizing potion. When her action became known, he exclaimed, "Would that you bore unto me only one more issue of the womb!"

As Rachel Baile notes: "Though Rabbi Hiyyah reacted with an outcry of grief, he did not challenge the legality of her actions." For Baile, this idea is critical for understanding the limits and choices that women face when making critical reproductive decisions. For our purposes, such texts complicate the straightforward pronatalist account and will be important for our study of oncofertility.

## Stewardship and Technology

Unlike other religious traditions, Jewish thought also demonstrates a complex relationship to the natural world and the use of technology to alter human "natural" fates. Because brokenness and suffering due to illness or accident are seen as problems to be addressed, and not primarily as suffering to be endured, technology that alters nature and alleviates human suffering is embraced by the tradition. It is also clear that the text and the reception of the text of genesis has been a pivotal event in how technology is understood. Consider this quote from J. David Bleich [6]:

> It is abundantly clear that human intervention in the natural order is normatively interdicted only to the extent that there are explicit prohibitions limiting such intervention. Moreover, there is no evidence either from Scripture or from the rabbinic writings that forms of intervention or manipulation not expressly banned are contrary to the spirit of the law. Quite to the contrary, Jewish tradition, although it certainly recognizes divine proprietorship of the universe, nevertheless gratefully acknowledges that while "the heavens are the heavens of God" yet "the earth has He given to the sons of man" (Psalms 115:16). In bestowing that gift upon mankind, the Creator has granted man dominion over the world in which he lives

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[5] Alert readers will recognize this interesting reversal of the usual case.

> and over the living species that are coinhabitants of that world. Man has been given license to apply his intellect, ingenuity and physical prowess in developing the world in which he has been placed subject only to the limitations imposed by the laws of the Torah, including the general admonition not to do harm to others as well as by the constraints imposed by good sense and considerations of prudence.

The mandate to heal is so strong that even apparently prohibitive texts can be circumvented with narrowly constructed literalist readings. For example, the texts that prohibit cross-breeding of animals and mixing of linen and wool might have been seen to prohibit genetic engineering. But faced with the problem that this would prohibit genetically engineered insulin, the decisors chose to limit the hukkim to only the animals mentioned. Bleich suggests a general principle, called "enough," based on a phrase in Genesis 17:1 in which God says "I, Shaddai" which is understood by a rabbinic word game as an acronym: *she-amarti-le-olami "dai"* (Who said to my universe "enough"). In making the created universe, God did not complete every task (the example Bleich gives is that God could have created plants with little loaves of bread hanging from them, but did not, instead creating wheat and allowing for the arduous breadmaking process to be in human hands. In this way, we are "finishers" of the work. (He also notes the eschatology of Shabbat 30b in which at the end of days, God will alter creation and finish it all off).

> In the interim, however, he has declared "Enough" i.e. he has precipitously interrupted the process of creation, and co-opted man, who must complete the process. [6]

In summary of the classic texts then, our initial research suggested that Jewish bioethics would support the research we had been asked to consider. Ethicists are asked to reflect on issues of ultimate meaning, for life and death decisions are a part of all healthcare choices, and such choices are a part of the normative discourse of the debate on human values that is the subject of ethics, not the sole concern of science, nor within the scholarly expertise of science. We argue and thus believe that we are "condemned to act," as Korsgaard, Kant, and Aristotle argue, meaning that we have to make moral choices as moral agents in all that we do and that there is not a neutral place that allows us to refrain from actions and their consequences. Thus, we understand that it is this action that defines our characters as "actors," persons, and as social beings. We explain to scientists that our world and ourselves are made by our work, and we seek to ask them what sort of selves and worlds their work is intended to bring. In summation, what can be said in general, about Jewish thought?

First we argue that oncofertility in general will be ethically acceptable because it is largely pronatalist and adheres to this aspect of the tradition. Sexuality within marriage is generally good; health is a nearly trumping value, but not the only value; there will be dissenting voices among, between, and within all traditions; and there will be a range of responses from liberal to conservative. Most Jews, like most Americans, experience moral actions as mediated by a view of themselves in relationship to others, and most Americans view life and death choices as also mediated and motivated by a view of themselves in relationship to God or Spiritual realities, often in terms of faith communities. All medicine and science take place in this context. Public science is funded by citizens who attend to moral considerations, and for Jewish thought, the major issue at stake in these considerations is not only the state of the embryo but social justice, treatment of the poor, widow, and orphan. Jewish thought asks after the "world to come" in two ways: by a text that sees children, families, and fecundity as signs of God's presence and that sees our work and what we make of the world as a decent place of habitation as another sign of our covenant with God. Texts are important for they set in place narratives, promises, and aspirations, and also because they create laws and norms that offer the chance to live in the world as it should be, not only accepting it as it is now.

## 2003–2006: The Joseph Project

When I first reflected on the project later named "oncofertility" it was before the project was funded or begun, and at stake was the problem of asking patients to participate in very tenuous, very speculative research. We called this research "the Joseph Project," named for the concept of storing seed against a dream's theory of scarcity and justice. At stake was the moral question: can a society use its resources to create a project that may never turn out to be needed, or may fail, purely on the basis of a speculation – a "dream." It is the question of nearly all of modern basic research. But it was made imperative by the urgency of cancer, which will steal the chance of fertility unless a swift intervention is made – the chance came only once, for patients will get a diagnosis and will begin therapy within days.

Our principle dream from our textual reading was to "bet on the dream" and make plans and policy in advance of possibility. Teresa Woodruff and her team had to collect data from patients long before results suggested by the research even in murine model. We used the text of the Joseph narrative as a source for this argument, noting that the Joseph stories are a core part of the Scripture texts of all Religions: Christiany, Islam and Judaism texts. Our question was the permissibility of speculative research.

The text:

> In my dreams I also saw seven heads of grain, full and good, growing on a single stalk. [23] After them, seven other heads sprouted – withered and thin and scorched by the east wind. [24] The thin heads of grain swallowed up the seven good heads. I told this to the magicians, but none could explain it to me. [25] Then Joseph said to Pharaoh, "The dreams of Pharaoh are one and the same. God has revealed to Pharaoh what he is about to do. [26] The seven good cows are seven years, and the seven good heads of grain are seven years; it is one and the same dream. [27] The seven lean, ugly cows that came up afterward are seven years, and so are the seven worthless heads of grain scorched by the east wind: They are seven years of famine.

The text then turns to who should oversee the plan:

> And now let Pharaoh look for a discerning and wise man and put him in charge of the land of Egypt. [34] Let Pharaoh appoint commissioners over the land to take a fifth of the harvest of Egypt during the seven years of abundance. [35] They should collect all the food of these good years that are coming and store up the grain under the authority of Pharaoh, to be

> kept in the cities for food. [36] This food should be held in reserve for the country, to be used during the seven years of famine that will come upon Egypt, so that the country may not be ruined by the famine.

We argued that this first, speculative research could proceed with careful oversight. In the next several years, however, our consideration of these questions deepened. It is to these evolving problems that the rest of the chapter will now turn.

## "Who Was It that Said Yes?" Emerging Research, Truth Claims, and Identity as a Question in Jewish Bioethics

Oncofertility, as a concept and telos, presented no serious violations of principle for Jewish ethics. My question is about the fragility and uncertainty of scientific knowledge and about who should have entrance into that knowledge – who is the verifier, who the watcher. I will use a narrative casuistry, using the literary halachic discourse to set in place a tentative response and to suggest a possible core principle in basic research, that of fidelity, which might guide our work at least as clearly as autonomy has shaped research ethics in the past and one possible method, that of *discordant narrative*, that might offer an addition to the Common Rule. Let us consider the case that first defined our work.

### *The Case*

The researchers faced a complex dilemma. As the research was initiated, each patient was not only told about the procedure and about the experimental nature of basic science, but that they would be kept fully informed about their tissue samples. In the process of the research, 80% of their tissue is frozen directly after surgery to be available for use should the research experiments prove successful. The other 20% is donated for research. There now is question of what to tell patients about the fate of the 20% of tissue that they donated to research as the research begins to yield results. Recently the protocol was rewritten, and now, like many protocols all tissues are de-identified, and researchers are not specific about the fate or condition of one person's tissue, phenotype, or genotype. In Northwestern University's genomic banking project samples, are stored and archived along with physical histories, but elaborate codes are kept to maintain complete anonymity. There is no relationship, between researcher and physician. In these cases, if a finding is uncovered that may impact a person's health, the plan is to give a generalized account of the research being done in the lab in the form of a newsletter that would alert all physicians and all subjects about the facts, with a vague, general admonition to seek private, non-research testing of personal genomes at personal expense. However, the first sets of Woodruff's patients were told that they would be kept abreast of their tissue status in a personal and direct way. The procedures are not anonymous – they are done by a known physician, the tissue is well labeled and each case is personal and contextual, and thus a great deal of information is known. In some cases, tissue “looks good” and the researchers are excited by this. In others, they consider the tissue, in the language of the lab “crappy,” meaning it is of visually poor quality. This is how all IVF and stem cell researchers talk – human eggs are graded like chicken eggs, on a scale of 1–4, with 1 being described “plump” and 4 generally being discarded, a scale entirely subjective, part of the oral tradition of the IVF clinic. But should they tell the patient, who is paying for tissue storage, for the other 80% and will pay, perhaps, for decades? At stake is it the language and initial promise can be changed for new patients, and if so, what is the duty toward the first patients? Do the researchers have to rediscuss and reconsent the patients and tell them of protocol changes? In plain terms they would have to explain why they are undoing a promise made to them.

The team is divided on how to proceed. The issue of disclosure may be one of the largest issues they face. There is a conflict between wanting to support full disclosure as a participatory model. Patients want to know what’s going on with what is an intimate part of their body, and upon which their future is engaged. In fact, the team will need to keep in contact with them for a long time to come and the question will inevitably be raised about whether it is realistic to hope for a genetic family. More issues will emerge, such as the problem of finding that she has genetic diseases that might affect fertility or that may cause her not to be able to reproduce with her own eggs, such as Tay Sachs, or oncogenes themselves. As more research uncovers more knowledge, the knowledge will become more important. But more knowledge may change the standards too. What if 5 years hence a new breakthrough is made and the “bad” tissue is no longer “bad” for it could be stimulated in some different manner. Once you begin to speculate about the future, either good or bad, then you are engaging in speculation of the most ephemeral sort, risking hype or fear-mongering. The fact that the knowledge base is mutable on all fronts means that any information is potentially misleading.

Moral appeals are made from many directions in this case, and we debate it fiercely. It is argued that patients cannot be allowed to think they have a therapeutic advantage from a clinical trial. Yet in this case, the entire premise is based on the sense of hope and promise, and is it a clinical trial at this point? If the research team ever moves to clinical trials for pregnancies, then it is precisely these women who will need to be recontacted and asked to be subjects. It would only be just thus, and of course you could not put non-matching embryos into women, for that would defeat the premise of the research. But to some extent, the tissue once separated from the patient as “research material” is now in a separate category – it is more akin to any other tissue or material used in basic research, such as HELA cells. Promises should be kept, we insisted, and telling the entire truth is important – this is their tissue, they are intimately connected to it, thus why hide relevant information as you learn it? In double-blinded clinical trials anonymity is key to remove bias, but in this case, is blinding possible or necessary? We remind them that minimizing harm and having compassion to the actual persons facing an actual human tragedy is a core value of medicine and we avoid paternalism by understanding that we cannot protect patients from “being upset” and thus do not hide difficult news. Should this be a part of our considerations? The problem is that patients and research subjects and tissue donors are all promised different things and the relationship varies. Their issues ideally should not be confused. Yet in this protocol – *they are all three at once at different times in the course of the experiment.* Is Northwestern University promising to act as the broker for "families after fertility", or is it using the tissue for a basic research trial? Are the doctors still the doctors of patients who are in clinical trials – especially if they will be the human subjects to first bear children from this protocol, should it work in the future? In this case, the research is deeply and inevitably intertwined with the lives of the women.

There are three options:

1. Maximal, transparent disclosure of all details of the procedure, outcome, and research findings as you proceed, including your complete sense of uncertainty.
2. Complete anonymity. A newsletter monthly on progress if desired and only if desired. An invitation to yearly or every 5-year review of the progress or lack thereof.
3. A combination of truthful elements with some information hidden, with full disclosure of what information is withheld.

## Humanities to the Rescue: The Text

We are faced with uncertain knowledge, and the deep uncertainty on every front, when seriously considered, threatened to destabilize the work. Here is where I turned to literature, in this case rabbinic literature to create a frame for our response:

> MISHNAH.
>
> THE OFFICER SAID TO THEM: GO FORTH AND SEE WHETHER THE TIME FOR KILLING [OF THE MORNING SACRIFICE] HAS ARRIVED. IF IT HAD ARRIVED THEN HE WHO SAW IT SAID: *IT IS DAYLIGHT!*
>
> MATHIA B. SAMUEL SAID: *THE WHOLE EAST IS ALIGHT*.
>
> *EVEN UNTO HEBRON?*
>
> AND HE ANSWERED '*YES*'.
>
> AND WHY WAS THAT [CONSIDERED] NECESSARY?
>
> BECAUSE ONCE WHEN THE LIGHT OF THE MOON ROSE THEY THOUGHT THAT THE EAST WAS ALIGHTAND SLAUGHTERED THE CONTINUAL OFFERING, WHICH AFTERWARDS THEY HAD TO TAKE AWAY INTO THE PLACE OF BURNING.
>
> It was taught: R. Ishmael said: The morning [star] shines. R. Akiba said the morning [star] rose.1 Nahuma b. Afkashion said: The morning [star] is already in Hebron. Who was it that said 'yes'? The man standing on the roof! Is he the dreamer and the interpreter? Should it, then, be he who is standing on the ground, whence would he know?
>
> If you like say it is he who stands on the roof, and if you like say it is he who stands on the ground. If you want to say it is he who stands on the roof; he says: THE WHOLE EAST IS ALIGHT, the one standing on the ground answering: EVEN UNTO HEBRON?

> Whereupon the former says: 'YES'. If you like say that it is he who stands on the ground: He says: THE WHOLE EAST IS ALIGHT? Whereupon the other responds: EVEN UNTO HEBRON? And the former answers: 'YES' [7].

What is going on in this text? Who are these people? The rabbis consider the case of having to make normative decisions based on realities of the natural world – when the sun comes up – in the face of uncertainty of stance and method and in the face of competing truth claims. At stake is when it is time for the first prayers and sacrifices in the morning. But there is a disagreement. Someone is standing on the roof, and someone on the ground. It is hard to tell who is who, and hard to deny anybody their claim – and we, readers, are watching of course. But the natural world is a difficult thing – yes, there will be clarity in the future, when everyone is awake and off to work, but now: has the morning star appeared? Is it alight?

As in medical research, there have been false sightings – the moon gave the appearance of the sun, there was a mistake, false hope, and the apparatus of healing and salvation – the temple service itself – was ramped up, in error. You must be careful – thus the two locations, on the roof and on the ground. But who said "yes?" they ask. Perhaps the guy on the roof, but perhaps not; perhaps the guy on the ground. One is the "dreamer, and the interpreter" and one decidedly not. But note that the answer is not given – only the instructions for how to conduct an argument. Whatever is said is countered – and that is the point – you need both locations to determine the reality. And in the text, the positions are changeable, uncertain who is who. Is it the dreamer and interpreter that confirms? Or the one on the ground? And who are we, the ethicists watching all of this? I am entirely uncertain of this point, of who is seeing the future better, more accurately.

The text suggests a role for ethics based in discord, counter narratives and discourse, and this is what we have found compelling about the project, the possibility of raising the discordant narrative. We did offer a recommendation, in our usually disagreeing about it way.

## The Recommendation: Here Is What I Wrote

> I recommended option one. It is resonant with moral appeals for full truthtelling. It fosters autonomy with the fullest respect for persons. It is consistent with the complex and multiple roles of the subjects. The tissue is, by definition, not anonymous, it is a part of a multiyear trial in which the subjects will need to be fully informed at all times. Adults should be able to decide what to do with their own body with the full range of medical and scientific information, including information about scientific uncertainty. I would urge you to reflect carefully on how robust your information is when you call a tissue "bad." Since you will be keeping closely in touch with your subjects, and since you would need to for scientific and medical reasons, the case is different than the collection of large libraries. In fact, the entire idea of genetic privacy is being challenged [8]. The research subjects in this case are not the equivalent of research subjects in clinical trials. They will need to be a part of the research itself, and because they will be enmeshed in the research as it develops. Their new status, tripled in moral location, requires a different set of relationships.

## Conclusion

In a world so uncertain, and in research conducted in the midst of tragedy so fraught, we have little, really to offer patients. Research is only the gaze, the observation, trying to see in the dark. What we have, we argued, is fidelity, meaning the promises that are made for as much clarity as possible. This principle works on all levels – I *promise* to tell you the truth, to tell you everything I know. In the text, the one on the roof needs the one on the ground; either one cannot exist as the sole narrator of the story.

Let me conclude by saying this works on many fronts and it goes for us, the researcher in ethics, as well. The fidelity we counseled between the participants and the researchers is as important as the acceptance of our different views. We have had significant struggles with some of the physicians, to whom we have promised only the certainty of our argument, not the certainty of agreement for whatever they do. In the last months, the NIH program officer reminded us that the research subjects are also the scientists, and even to tell this story needs a signed consent form my researcher, my friend who I study. I imagine myself handing the form up to her to sign, she is on the roof, I am on the ground. Or is it the other way? Who says yes?

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# Part V
# Ramifications for Education and Economics

# Chapter 25
# The Oncofertility Saturday Academy: A Paradigm to Expand the Educational Opportunities and Ambitions of High School Girls

**Megan Faurot and Teresa K. Woodruff**

## Introduction

The Oncofertility Saturday Academy (OSA) is a high school education program born out of the work of the Oncofertility Consortium. The Oncofertility Consortium was created to overcome roadblocks that exist between reproductive biologists, fertility specialists, and oncologists in order to provide fertility options to young women, men, and children with a fertility-threatening cancer diagnosis or treatment. Many cancer patients who are in their reproductive years, who we define as oncofertility patients, have limited time to make a decision about fertility preservation before beginning their cancer treatment. Supporting the oncofertility patient decision-making process with improved fertility preservation options is the driving force to translate knowledge from the "bench" to the "bedside" for the Oncofertility Consortium. The Oncofertility Consortium is also investing in the next generation of potential scholars in the field, which guided, in part, the creation of OSA.

Traditionally, translational research is defined as the transfer of new knowledge gained in the laboratory setting, the "bench," to the human (TI) and the enactment of the results of the clinical studies into everyday clinical practice, the "bedside" (T2) [1]. The slow pace of translational research and the lack of rapid advancements into the clinical setting have been described as the T1 and T2 roadblocks [1]. The Oncofertility Consortium directly addresses the T1 and T2 roadblocks; however, it became apparent that the translational science paradigm was missing a domain: the "desk" (T0). The "desk" represents the acquisition of knowledge and skills through learning experiences that a student needs to successfully pursue careers associated with the "bench" or the "bedside." The roadblock of this domain, T0, exists between the "desk" and careers in science and hinders more women and minorities compared to white men. Research has shown significant attrition of girls and minorities, who, though interested in science and consider a career in science, change their career trajectory during the critical transition period between high school and college.

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According to the September 2006 National Academy of Science report, Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering, "Fewer high school senior girls than boys state a desire to major in science or engineering in college. Girls who state such an intention are likelier than comparable boys to change their plans before arriving at college [2]." The implications of the T0 roadblock are manifested in the science workforce. The National Science Foundation reported that between 1980 and 1990 the percentage of women scientists and engineers in the United States increased from 13 to 22% [3]. More recently, in 2006, women in the United States made up 44% of the labor force, but still only 26% are scientists and engineers [3]. The stratification of racial/ethnic representation of women scientists and engineers in 2006 was approximately 70% White, 18% Asian, 6% Black, 5% Hispanic, and 1% Native American/Alaskan Native [3].

The Congressional Commission on the Advancement of Women and Minorities in Science, Engineering, and Technology Development issued a report in September 2000, Land of Plenty: Diversity as America's Competitive Edge in Science, Engineering and Technology, which identified multiple causes to explain the attrition of girls and minorities from the science pipeline between high school and college [4]. One explanation cited the lack of appropriate role models who provide a positive influence in supporting students to make decisions about their academics and career as a factor in the underrepresentation of women and minorities in the science workforce [4]. As a result of women and minorities never being equally represented in science, stereotypes of women's capabilities in science developed and influenced individuals and cultures of societies. These stereotypes can affect how girls and minorities perceive themselves and what they think they are capable of achieving academically and professionally.

Additionally, the coupling of stereotypes with the lack of qualified science teachers and access to high quality science education in precollege education [4] means that girls and minorities are not enabled or supported to pursue science. According to Taking the Pulse of Bioscience Education in America: A State-by-State Analysis, a report released in May 2009 by Battelle, the Biotechnology Industry Organization and Biotechnology Institute, that the United States' middle and high school students are not performing at a level in their life science courses that indicate their ability to succeed and be competitive in bioscience careers [5]. In addition, the report indicated that fewer students express interest in science because of the education they receive in their science classes [5]. Precollege science educators have a responsibility to deliver engaging curriculum to both encourage and prepare students to take science courses in college. The number of potential scientists that are simply being lost due to circumstances beyond their control in middle school and high school is a serious problem that needs immediate focus and aggressive intervention. At Northwestern University (NU), the Oncofertility Consortium created OSA, a program to inspire and prepare the next generation of scientists and clinicians (Fig. 25.1). OSA has addressed the T0 roadblock with small cohorts of high school girls since 2007.

This chapter will describe the OSA program and practices and its investment in parents and the alumni of the program, as well as illustrate how the OSA model can

> *"This program has given me so much motivation and inspiration to become a doctor. It gave me the insight that I needed to be sure that I wanted to become a doctor."*
>
> High School Student 2008

**Fig. 25.1** A senior learning how to examine the heart with the help of her female medical student mentor

be applied to any area of science and be used as a template for national expansion. We believe the OSA model contains the working formula to combat the T0 roadblock to eventually cause an increase in the number of girls who are interested in science and decide to remain in the science pipeline.

## The Development of the Oncofertility Saturday Academy (OSA)

To achieve diversity in the science workforce, aggressive, early intervention approaches need to be implemented to enhance the current educational system. To combat the root causes of the T0 roadblock, OSA was built on four interrelated practices: (1) high school–university science partnership; (2) authentic and relevant science learning modules; (3) science mentor and support network; and (4) web-based science communication platform (Fig. 25.2).

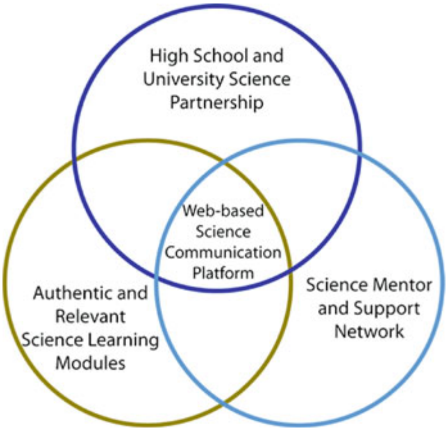


**Fig. 25.2** The four interrelated practices of the OSA to overcome the T0 roadblock of translational science

OSA was initiated in 2007 as a science partnership between NU and Young Women's Leadership Charter School (YWLCS) of Chicago. Teresa Woodruff, Ph.D., the Thomas J. Watkins Professor of Obstetrics and Gynecology at the Northwestern University Feinberg School of Medicine and Megan Faurot, M.Ed., the Director of Education Programs at the Institute for Women's Health Research co-direct OSA. In its first year, OSA targeted 11th and 12th grade students from YWLCS who expressed interest in considering a career in science or medicine or who were undecided on a career path but demonstrated either a curiosity toward science or who excelled in their science classes. Fourteen girls from the 11th grade and two girls from the 12th grade were selected to participate in the first year of the program. During the first year of the program, the focus of OSA was the basic science research of the emerging field of oncofertility. Over three consecutive Saturdays in the month of February, three working laboratories at NU opened their doors and deployed their scientists to deliver authentic learning experiences that focused on reproductive science, cancer biology, and oncofertility. In addition to the laboratory activities, students met with staff from college admissions to learn about the college application process and toured NU's undergraduate campus to gain exposure to college life. To mark the successful completion of OSA 2007, YWLCS hosted a small, intimate graduation for the students to celebrate their new knowledge with their parents and program directors. At this event, the 11th grade girls inquired what opportunities were going to be available to them as 12th graders – as a result, the expansion of OSA to include a second year that focuses on the clinical applications of oncofertility was initiated.

Since 2008, OSA has been delivered as a 2-year program that runs during February and March. Eleventh grade students are invited to participate in Junior Oncofertility Saturday Academy (JOSA), and 12th grade students join Senior Oncofertility Saturday Academy (SOSA). The structural components of the JOSA and SOSA program model consist of a student selection process, an informational meeting, after school workshops, Saturday modules, and a graduation ceremony.

Student recruitment for OSA targets 11th or 12th grade students who express curiosity about science, contemplate a career in science, perform at a proficient level in their academic courses, and pass their current science course. The application process requires submitting an eight-page application consisting of essay questions, a copy of their current academic transcript, teacher recommendations, parental support form, and student commitment. The application is reviewed by a panel of individuals from YWLCS and NU. Qualifying students are then asked to interview for the program. Following the interviews, 32 students are selected to participate in the program – 16 students for JOSA and 16 students for SOSA. The students invited to OSA have diverse academic abilities, interest levels in science, career goals, and racial/ethnic backgrounds. Students who are selected into JOSA are highly encouraged to continue with the program during their 12th grade year; however, they are not guaranteed a slot in SOSA. Previous JOSA students need to reapply to participate in SOSA.

Selected students and their parents then attend the mandatory OSA informational meeting where they are officially welcomed to the program. OSA materials are distributed to the students and an overview of the OSA calendar of events and modules is given. Parents review and sign permission forms and web developers introduce the OSA website and give a brief tutorial to demonstrate how to navigate the website.

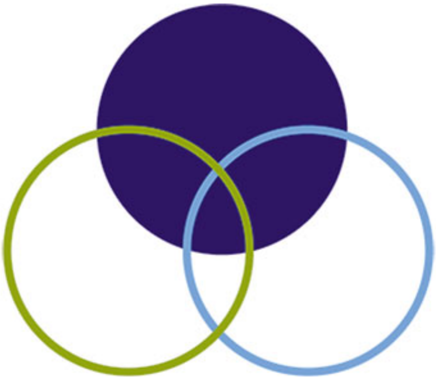
The OSA curriculum is delivered during after school workshops and Saturday sessions. The after school workshops are held at YWLCS and co-taught by Megan Faurot and the YWLCS science teacher. The after school workshops are 2 h long and held on either the Tuesday or the Thursday prior to the 8 h long Saturday sessions at NU. The after school workshops prepare the student with relevant background information and skills to fully engage in the Saturday sessions. JOSA and SOSA each have four Saturday sessions, which consist of college-level lectures, laboratory and clinical activities, and college- and career-focused discussions given by scientists, clinicians, and other professionals in the field.

Parental support and active involvement is a key element of OSA. In 2009, OSA offered the Parent Oncofertility Saturday Academy (POSA) to provide parents the opportunity to play an active role in their daughters' interests in science and medicine. The JOSA, SOSA, and POSA curriculum is described in the "Authentic and Relevant Science Learning Modules" section of this chapter.

Lastly, OSA students learn and practice how to effectively communicate scientific information by creating summative group projects. Written and verbal communication skills are needed to thrive and compete in the field of science. Time, workspace with computers, and other supplies are provided to the students who work in small groups to create projects that demonstrate and communicate the new knowledge and skills gained by participating in OSA. The final group projects are posted on the OSA website, presented at YWLCS events and academic functions, and showcased at the OSA graduation to share with the OSA faculty, their peers, family, and communities. The OSA graduation provides the students with the opportunity to celebrate their new knowledge and skills.

## Practices of the Oncofertility Saturday Academy

### *Practice #1: High School–University Science Partnership Model*



A science partnership between a high school and a university creates a continuum of science education that benefits both students and educators [6]. High schools that establish partnerships with a university create an opportunity for students to be exposed to real college science before their undergraduate freshmen year [6]. It has been shown that girls who are interested in science often change their minds during their first year of college [7]. Girls who successfully earned a science degree in college indicated that they received encouragement from their parents and high school teachers [7, 8]. Another significant factor that encourages girls to stay in science is the opportunity to experience laboratory research during their freshmen year [8].

The science partnership model between NU and YWLCS, initiated in 2006, is one of the four practices that are crucial to the success of the OSA (Fig. 25.3). The idea was to collaborate between two academic institutions – a public high school and a private university – that are both committed to education and achieving academic excellence in women and girls. Each institution provides essential factors that enable this mutually beneficial science partnership to flourish. Northwestern University, a premier research and teaching institution, provides state-of-the-art research facilities and a pool of scientists, clinicians, and graduate/medical students who are committed to the growth and advancement of the science community. YWLCS inspires urban girls to engage in rigorous college preparatory learning in a small school focused on math, science, and technology that nurtures their self-confidence and challenges them to achieve. Students who attend YWLCS come from 30 underserved communities in Chicago. The student population of YWLCS consists of 78% African American, 15% Latina, 6% Caucasian, 1% Mixed Race, and 1% Asian. Eighty percent of the girls who attend YWLCS are eligible for free or reduced price lunch.

NORTHWESTERN
UNIVERSITY

Young Women's Leadership
Charter School
of Chicago Girls of today, leaders of tomorrow.

*"Continue this great relationship (between Northwestern University and Young Women's Leadership Charter School) so it can become a model for other schools throughout the world. The impact of this relationship is getting more girls, like my daughter, involved in science earlier on and opening their eyes to the huge spectrum of possibilities in the field of science. Thank you."*
Mother of OSA Student

**Fig. 25.3** Northwestern University and Young Women Leadership Charter School science partnership was initiated in 2007

## Partnership Role of NU

To prepare for the 15 JOSAs and 15 SOSAs, there are over 100 NU and YWLCS faculty and staff, called the OSA faculty, involved in the planning and delivery of OSA. The OSA co-directors lead the development and coordination of OSA with NU and YWLCS. The OSA faculty work together with the OSA directors to design engaging, inquiry-based learning experiences for the students. NU is responsible for preparing and providing all the educational and logistic program materials needed for OSA. To determine the effectiveness and impact of OSA, NU developed assessments that are administered pre-, during, and post-OSA. Based on the results of the assessments, each year the OSA curriculum is enhanced to improve student learning and experiences. For example, the OSA website was constructed during the third year of OSA to improve the dissemination and sharing of program materials and information with the students, parents, and faculty. More information about the OSA website can be found at whsp.northwestern.edu and in the "Web-Based Science Communication Platform" section of this chapter.

## Partnership Role of YWLCS

YWLCS commits to a number of other responsibilities to maintain the partnership with NU. YWLCS identifies a science teacher from the YWLCS science department to serve as a partnership coordinator for OSA. The partnership coordinator acts as the liaison between the students and the scientists and clinicians of OSA by supporting NU with the student selection process, student and parent communication, and after school workshops. The OSA after school workshops occur at YWLCS on the Tuesday or the Thursday before the Saturday sessions. One of the OSA directors works with the partnership coordinator to co-teach the after school workshops to prepare the students for the Saturday sessions. During the Saturday sessions, the partnership coordinator supports and guides the students learning by connecting it to the concepts and skills covered in the science curriculum at YWLCS (Fig. 25.4). The partnership coordinator's presence is key during the Saturday sessions because she is able to provide the NU scientists and clinicians insight into the students' prior knowledge. This helps them determine what type and level of questions to ask the students to construct their new knowledge. By attending the Saturday sessions, the partnership coordinator gains new scientific knowledge and access to resources and tools that can be integrated back into classes to enhance the science learning for all the girls at YWLCS. Lastly, the partnership coordinator advises and works with

*"This program has provided me with the opportunity to stay connected to the current research findings and developments in the field of science. The scientific knowledge and resources I am exposed to through this program have helped me develop more engaging and relevant lessons so all of my students are more excited and curious about science."*

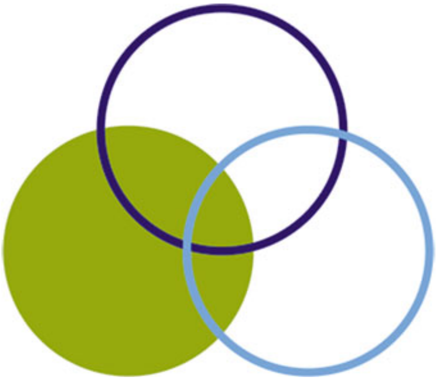
YWLCS Science Teacher

**Fig. 25.4** YWLCS science teacher provides guidance to two high school students during a JOSA Module 3 laboratory activity to study fertilization the OSA students to present their group projects at a variety of YWLCS events and academic functions.

### Shared Partnership Roles of NU and YWLCS

NU and YWLCS are equally invested in developing and sustaining the science partnership through OSA. NU works with the YWLCS science team to identify how the OSA curriculum aligns with and enhances the YWLCS science curriculum scope and sequence. The idea is that providing OSA to YWLCS students will enable the YWLCS science department to meet and exceed state and national science standards. NU and YWLCS also collaborate on the review board that selects the OSA students. Regular communication with the OSA students, alumni, and parents is an effort that both institutions contribute to in order to develop the relationships that make up the OSA family. Both NU and YWLCS share responsibility of contributing funds to cover the operating cost of OSA.

## *Practice #2: Authentic and Relevant Science Learning Modules*



Oncofertility is an interdisciplinary and interprofessional approach to developing and providing new fertility preservation options to young men, women, and children who have been diagnosed with cancer or other serious diseases and must undergo potentially fertility-threatening treatment. There are two main reasons for focusing OSA on oncofertility. First, oncofertility is a new, exciting area of science. Exposing high school girls to an area of science so new that it has not yet made it into their high school biology or anatomy textbooks is powerful. The girls are able to experience firsthand how science concepts and technologies are developed and practiced in both the basic science laboratory and the clinical settings. For the most part, the high school girls have learned science directly from their science textbooks, which we refer to as “horizontal learning.” In OSA, the students are able to experience science before it even reaches the science textbooks, which we refer to as “vertical learning.” The girls experience authentic scientific inquiry because there are multiple questions that still need to be answered regarding oncofertility; they work alongside the scientists who are developing techniques and procedures to answer these questions. Second, oncofertility emphasizes the female reproductive axis. The high school girls are empowered by the knowledge they gain about the anatomy and physiology of their own reproductive system. The girls gain a far more in-depth understanding of the female reproductive system than they receive in typical health or sex education courses in school. Moreover, OSA broadens their understanding of the function and purpose of their reproductive system as more complex than just sex and pregnancy; because of this knowledge and awareness, the OSA girls are able to make informative, authoritative decisions about their general and reproductive health.

OSA offers six challenging, thematic learning modules for the high school girls to explore the fields of reproductive science and cancer biology within the context of oncofertility. JOSA consists of the three basic science research modules and SOSA consists of three clinical application modules. Students participate in group projects to practice communicating scientific knowledge and demonstrate what they learned about oncofertility in the laboratory and in the clinical setting. The final module of OSA, the Parent Oncofertility Saturday Academy (POSA), is repeated both years. POSA is designed for the students and parents to share common science experiences that focus on the field of oncofertility, academic degrees, and careers in science.

The OSA girls and their parents are offered multiple learning experiences over the 2-year period in order to help them identify and define their academic and career pursuits. Girls who intend to major in science in college are less likely to have well-defined science career goal than their male counterparts [9]. In addition, the science concepts covered in OSA are highly advanced with the intent to prepare them for the rigor of college science courses. Rigorous study in high school is the best indicator that a person will receive a degree in college [10]. In particular, taking advanced mathematics and science courses during high school has been shown to be an indicator of college success for students of all races and ethnicities who pursue science degrees in college [11, 12].

As the students experience the modules, they learn how the basic science research is translated into clinical practice in the field of oncofertility. Each OSA module is structured with a set of learning outcomes and guiding questions to focus the students. OSA modules consist of both an after school workshop and a Saturday session. The after school workshops are held at YWLCS and are led by secondary level science teachers. As mentioned in a previous section, the after school workshops occur prior to the Saturday sessions at NU to prepare the students with important background information and skills. The Saturday sessions are held at NU and are led by scientists and clinicians who are conducting oncofertility research or providing care to oncofertility patients. College-level lectures, laboratory or clinical activities, and a variety of other workshops make up the Saturday sessions. A student who participates in both years of OSA spends a total of 22-h in the after school workshops and 64-h in the Saturday sessions. Seventy-five percent of OSA occurs on NU's campus. The idea is to expose the girls to the potential next steps of their academic and career paths. Built into the OSA curriculum are college-level lectures by university professors, a campus tour, and discussions with undergraduate admission counselors and students. The settings of the Saturday learning experiences occur in the state-of-the-art research and clinical facilities of NU and Northwestern Memorial Hospital. Students are able to observe firsthand and work alongside real scientists and clinicians.

## Junior Oncofertility Saturday Academy (JOSA) Modules

JOSA consists of three modules that focus on the basic science research of oncofertility that occurs at the "bench."

### Module 1: Regulation of Ovarian Function

Oncofertility is introduced to the students by studying how scientists test fertility preservation methods for women. Students become familiar with the anatomy and physiology of the female reproductive system. Dissections of mice are performed to identify the structures of the reproductive system and compare their observations to the human reproductive system. Students remove the ovaries from these mice and learn how to isolate and identify follicles at different stages in the ovarian cycle. As the students observe the follicles, they are challenged with the question of how can follicles isolated from the ovary be matured into an egg outside of the body? This question is addressed as the students learn how to encapsulate follicles in aliginate beads. As the students practice follicle encapsulation, scientists explain that the process has resulted in live births of mice and is currently being tested in chimpanzees. Scientists share with students that the goal is to translate this fertility preservation method into clinical practice for the oncofertility patient. The potential of this technology impacting human life raises many ethical questions. After the laboratory activities, the students participate and ask questions in a bioethics workshop that outlines the major ethical issues associated with the discipline of oncofertility.

### Module 2: Gene Expression in the Ovary

Students engage in learning experiences to understand that providing fertility preservation options for women is dependent on the function and development of the ovary at the molecular level. The girls learn how scientists detect genes and proteins in the ovary. They are introduced and guided by scientists to conduct multiple laboratory protocols and use scientific equipment during this module. The scientists guide the students step by step as they isolate (Fig. 25.5), amplify, visualize, and analyze DNA from genetically engineered mice. Techniques practiced by the students include DNA isolation, polymerase chain reaction, and gel electrophoresis. Students perform immunohistochemistry and fluorescence microscopy to understand how scientists determine and measure protein expression in the ovarian tissue.

### Module 3: Fertilization and Beyond

Students explore how in vitro fertilization technologies contribute to creating options for preserving fertility. To study fertilization, the students are now introduced to the male reproductive system – until this module there has been sole emphasis on the female reproductive axis – and conduct lab activities to observe fertilization in real time of both sea urchins and *Xenopus* frogs. Fertilization of both of these animals occurs externally making them both effective learning models to

**Fig. 25.5** A JOSA student observing isolated DNA with a scientist

study the process of fertilization and the meaning of the term in vitro fertilization. To track the early embryonic development of the frogs, the students learn the technique of embryo microinjection with a fluorescent protein and how to analyze the results using fluorescence microscopy.

## Senior Oncofertility Saturday Academy (SOSA) Modules

SOSA consists of three modules that focus on the clinical applications of oncofertility that occur at the "bedside." Explicit connections between first and second year of OSA are integrated into the curriculum. The purpose is to create a continuous learning experience for the students to learn about the nature of translational science.

### Module 4: Eggs, Sperm, and Embryo, Oh My!

This module models the shift that occurs in the translational science of oncofertility, from the "bench" to the "bedside." To connect the learning experiences from the first year to the second year of OSA, the students compare and contrast mouse sperm to human sperm. The difference in the structures and functions between the animal and human models that the students observe affirms that the application of basic science research to clinical practice is a challenging process. Students conduct a laboratory activity to test the importance of using a cyroprotectant when freezing human sperm. The conclusions drawn from this laboratory activity are used to discuss the development of freezing methods for the human egg. The students explore fertilization and embryo development of preserved egg and sperm by observing mouse embryos at various stages before implantation. To provide the girls with a framework to ask questions and share thoughts connected to ethical implications of the oncofertility clinical applications, a bioethicist facilitates a discussion after the work in the lab.

### Module 5: Oncofertility and Surgery

To fully understand the oncofertility patient, students learn about the development of cancer and outline how cancer treatment options threaten fertility. Students discuss the options available to oncofertility patients and how surgery is an option for some to preserve their fertility. Surgeons use surgery videos to demonstrate how they remove ovaries from an oncofertility patient. Connections to the students' dissections of the female mouse, during the first JOSA module, are made to show the translation of science from the "bench" to the "bedside." Surgical procedures and instruments used to perform the removal of ovaries from oncofertility patients are described, compared, and simulated. Students learn how to use suture instruments to make simple interrupted and running continuous closures. The laparoscopic simulators that surgeons use to practice their techniques are made available for the students to learn how to manipulate. Students enter into a real operating room that is equipped with the da Vinci robotic surgical system. Students are able to practice using the da Vinci robot to experience how it works and discuss how they think it is an advancing surgery (Fig. 25.6). Lastly, students take their surgical experience and apply it to hypothetical oncofertility surgical case studies. In small groups, students discuss the case, and like real physicians, they decide the best option for this hypothetical patient.

**Fig. 25.6** A SOSA student observing how the da Vinci robotic surgical system works

### Module 6: Doctor for a Day

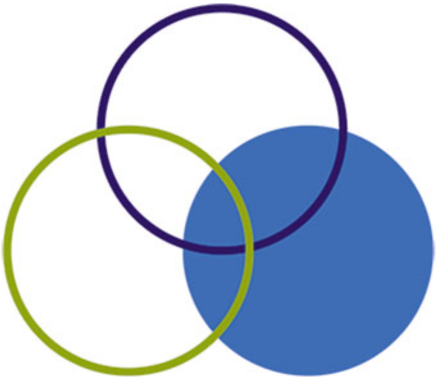
Students learn how a physician would examine a patient during a physical exam. To set the stage, a patient navigator presents oncofertility patient case studies to the students. The patient navigator explains that it is often during a regular doctor's appointment when the first symptoms of cancer are observed. The students are then paired with female medical school students who guide them as they learn how to take vital signs, radial pulse, and blood pressure and to perform self-breast exams, bimanual pelvic exams, pap smears, and heart exams using a dummy/model.

### Module 7: Parent Oncofertility Saturday Academy

The Parent Oncofertility Saturday Academy (POSA) was designed and implemented into OSA in 2009. The purpose of adding this module to the sequence was to provide time for the students to share their experiences with their parents or other family members. Each student can bring two family members to this module. Together, the students and parent rotate through laboratory, clinical, and classroom workshops, which replicate the learning experiences of the students in Modules 1–6 (Fig. 25.7). The module then focuses on the variety of science and medical academic programs and career options and information about funding opportunities and coursework requirements needed to pursue degrees in science and medicine is provided. Lastly, the students, parents, and facilitators participate in an open forum and evaluation to discuss and share their OSA experiences in order to contribute to the development and improvement of OSA.

**Fig. 25.7** Parent learn how to make aliginate beads during POSA

## *Practice #3: Science Mentor and Support Network*



Developing a multifaceted science mentor and support network can overcome the T0 roadblock by connecting members of high school and university communities [13]. Members from the high school and the university who are actively involved in the program include the high school girls, alumni of the program, high school science teachers, parents and family members, female medical students, scientists, and clinicians. By actively involving members from the high school and university communities, OSA is building a synergistic science support network to foster more high school girls' interest in science during the transition period between high school and college. The members of the science support network provide a wide range of support including mentoring, advising, and role modeling. Additionally, approximately 75% of the medical students, scientists, and clinicians who are involved in OSA are women; thus, the students are able to identify with the women who are involved in this program, view them as role models, and establish mentoring relationships with them. Such relationships have been shown to have significant influence on guiding girls who are interested in science through the many academic and career choices [14].

Communication is the essential element to building and sustaining the science mentor and support network of OSA. Within OSA, communication lines are either newly created or, if they are already established, given new purpose to increase the frequency of use. OSA facilitates high school science teachers' communication with students and parents regarding science, preparation for college science, and science careers and encourages parents and their daughters to have science-related conversations. OSA creates the experiences and the platform for girls, their families, and scientists to meet and learn from each other.

## OSA Supports Students, Parents, and Faculty Development

### OSA Students and Alumni

The high school girls who participate in the program are committed to working together to conduct hands-on investigations, perform clinical simulation, and create scientific poster projects. The girls also share common experiences such as wearing matching laboratory coats and scrubs, traveling together between their school and the university, and eating meals together. These shared experiences create an empowering bond between the girls that has been coined the "science-sisterhood" (Fig. 25.8). Amazingly, girls who are in seventh grade at YWLCS have become

> *"This program has created a bond, a sisterhood between girls that can never be broken. We are going to be the leaders of tomorrow and are going to need strong sisters to help each other along the way."*
> High School Student, 2009

**Fig. 25.8** High school students who participate in OSA call each other "science sisters" aware of this "science-sisterhood" and aspire to become a part of this program. The outcome of this "science-sisterhood" is a cohort of girls who have similar career goals and who support each other to stay focused and committed to excelling in school and participating in OSA.

The girls who participated in the program during high school and are now college students continue to play a key role in the development of the science support network. As college students, they directly interact and support the high school girls by volunteering their time to be alumni leaders during the OSA modules. Soon, OSA alumni will participate in bi-annual focus groups to evaluate how the program impacted their transition between high school and college and allow them to share their challenges and successes in achieving their goal of pursuing a career in science. The OSA alumni will also be invited to NU to engage in daylong events during their winter and summer breaks from college. These gatherings will provide the OSA alumni with the chance to reconnect with their peers and program facilitators.

### OSA Women Scientists, Clinician Role Models, and Near-Peer Female Medical Student Mentors

As mentioned, approximately 75% of the scientists, clinicians, and other professionals who are involved in the delivery of OSA program activities are women. Providing girls with multiple opportunities to work alongside women scientists and clinicians who have successfully reached a career in science gives them the confidence to continue to pursue their interests in science (Fig. 25.9). As a result of the small size of the each cohort (16 students), the girls are able to directly communicate with the female role models. Through these interactions the girls gain valuable scientific knowledge and learn how other women were able to successfully reach their goals of becoming leaders in science.

OSA actively collaborates with an established NU women's medical student group associated with the American Medical Women's Association. Each high

*"This program inspired me to keep working towards my dream of becoming a surgeon. The women scientists and doctors that I met through this program showed me that yes we are great and yes we can do anything that we set our minds to."*

High School Student 2008

**Fig. 25.9** An NU physician showing two seniors how to use the laparoscopic simulator school girl is paired with a female medical student throughout the program. The result of these pairing is the development of "near-peer" relationships with women who are in the process of pursing a medical career. We have observed that providing dedicated and focused time for the girls to communicate with these female medical students, in both informal and formal educational settings, has helped and encouraged the girls to define their own academic and career goals. These female medical students are key role models for these girls because if the girls stay focused and committed to their desired academic and career goals, they, too, could be women medical students.

### OSA Parents and Family

Parental involvement has been an underlying reason for the success and growth of OSA. OSA is designed to build relationships with the parents and support the development of the parent science network and the parent–daughter relationship. This parental engagement begins before the students are even accepted into the program. There is a parent support form that each student needs to submit with their application that is used to gather parent contact information and to outline three areas of support that are expected from the parents throughout the program: (1) laboratory support; (2) time and travel support; and (3) active participation. The laboratory support statement asks the parents to give their daughters permission to work in the laboratory and in clinical settings and to agree that their daughters must conduct themselves in a responsible and professional manner to ensure the safety of others. The parents then commit to making necessary arrangements for their daughters to arrive on time to all the program events. If an unexpected situation occurs (i.e., illness, family, or personal emergency), the parent or student needs to contact the OSA directors or partnership coordinator. Lastly, the parents commit to actively participate in the three OSA events that they are invited to attend – the informational meeting, POSA, and graduation. If they are unable to attend an event, they are expected to identify a family member or adult to represent them in their absence. The parent support form demonstrates to parents, from the very beginning, that OSA values their involvement with and support of their daughters throughout the program.

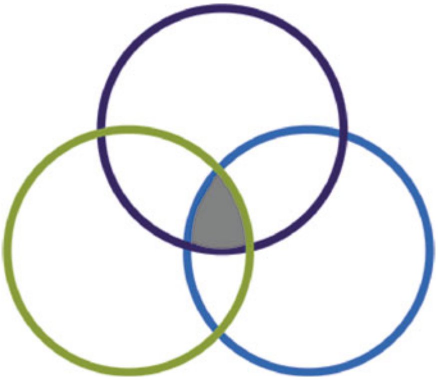
This relationship between the OSA and the parents continues through regular communication by phone, Internet, or personal interactions at the three OSA events they are invited to attend. In addition, OSA parents develop relationships among themselves and create a network in which they are able to exchange experiences and accumulate information to become stronger advocates for their daughters. Parents are thus equipped with the awareness and knowledge to communicate more effectively with their daughters about their interests and pursuits in science. Many of the parents have shared that what they gain from OSA is both valuable and useful because they either did not attend college or are not science professionals. OSA creates a direct portal for high school girls and their parents who are socioeconomically disadvantaged to have access to resources and opportunities that are not typically embedded in their social network [15]. The exposure provided by OSA is expected to leverage the students' prospects onto a path of science and success.

> *"This parent workshop was very helpful. I feel more prepared to support my child in making decisions about her future goal of becoming a scientist."*
>
> *Father of High School Student, 2009.*

**Fig. 25.10** The OSA Family including students, parents, and directors at POSA

Collectively, the students, role models, mentors, and parents amalgamate to form the OSA family (Fig. 25.10). The OSA family members are bonded together by science and success. OSA creatively brings together members of society with varying social demographics and educational backgrounds to solve the problem of attrition of girls of all races and ethnicities from the science pipeline. Together the OSA family focuses on preparing and supporting the next generation of potential women science leaders.

## *Practice #4: Web-Based Science Communication Platform*



An interactive website was constructed to develop a web-based science communication platform to enhance OSA in multiple ways. The website is a distinct practice of OSA but also directly interconnects the three other practices of OSA – high school and university science partnership, science learning modules, and mentor and support network. There are three goal areas of the OSA website: (1) to share and distribute information about the program; (2) to increase and improve the communication and relationship-building interactions with the students of the program; (3) to broaden the pedagogical strategies of the program to extend the students' learning into the virtual setting. To accomplish these goals the OSA directors worked in collaboration with web developers from the Northwestern University Advanced Media Production Studio. The construction of the OSA occurred in two phases. Phase one was the construction of the pilot website for the OSA 2009. Based on user feedback, phase two was initiated and will be completed for OSA 2010. The current development in OSA website tools and features and their utilization to carry out the goals are outlined in this section.

Public and secure interfaces were built for the OSA website for information to be uploaded and accessed for targeted audiences. Students, parents, teachers, faculty, academic institutions, and donors were the identified targeted groups of users. The type of information and how the users would navigate the site to retrieve information were thoughtfully considered during the design phase of the website. The public domain is accessible to any persons interested in obtaining information about the program but designed specifically for our targeted users. The OSA website consists of multiple informational pages (i.e., About OSA, OSA Students, OSA Parents, OSA Faculty, OSA Curriculum, and OSA Multimedia). To describe a few of these informational pages, the About OSA informational page provides an overview of the program structure and goals, calendar of events, announcements, and latest news. The OSA Students informational page consists of a series of questions to inform students about eligibility, the recruitment and selection process, and what is expected if selected into the program. The OSA Faculty informational page consists of a searchable mechanism to view and learn background information about the faculty who deliver the curriculum. Lastly, the OSA Curriculum informational page provides a selected sample of the curriculum materials and, if interested, instructions on how to learn more about the curriculum.

The OSA website consists of two secure domains, one for students and one for the OSA directors and faculty, that require a username and password to enter. It is within the secure interface that the communication and pedagogical tools can be accessed, utilized, and maintained. Making these tools accessible only through the secure interface allows for regulation of how they are used and distributed. Students have secure access to the student communication portal, student profiles, and the full curriculum. Through the secure domain the OSA directors and faculty have the administrative access and functionality to upload new content and utilize the communication portal.

The communication portal of the OSA website was built to increase and improve the communication with the OSA students. Regular and continuous communication is a key to building relationships with each individual girl and ultimately a network of girls who are interested in science. Each of the OSA students is given a virtual space, a student profile page, to share academic- and professional-focused information about who they are including their interests, extracurricular activities, academic goals/activities, career goals/activities, and contact information. The OSA students have access to each other's profile pages to comment and exchange information. Information the students add to their profile page can easily be used or transferred to a resume or application while applying for college or a job. Students start to create these profile pages once they are selected into OSA and are encouraged to maintain and update the information as they transition into college and beyond. Directors and coordinators of OSA regulate the contents added to the students' profiles using a feedback mechanism tool. This feedback mechanism tool allows the directors and coordinators to review the students' contents and provide critical feedback, advice, and encouragement to them through this virtual medium.

All modes of communication are used and encouraged in OSA – in person, phone calls, text messages, and email exchanges. To maintain and develop relationships with the students, it is important to track the type, frequency, and duration of communication with the OSA students. To document and maintain accurate communication records is a challenge for two reasons: (1) the network of girls continues to increase annually and (2) multiple members from the high school and university communicate regularly with the girls. Built into the OSA website is a communication log system that the directors, coordinators, and mentors can access to record and update information about individual students.

To broaden and extend the students' learning beyond the physical space of the classrooms, clinics, and laboratories, pedagogical strategies are features built into the OSA website. Accessible through the secure communication portal is a web-based forum. As mentioned in the "Authentic and Relevant Science Learning Module" section of this chapter, there are a total of 86 direct instruction hours (22 h in after school workshop, 64 h in Saturday sessions) of OSA. During this direct instruction hours the students are exposed to new and challenging information. The directors and coordinators generate topics and questions for the OSA website forum to provide a space for students to process and reflect on the science content and skills, mentoring, college, and career exploration that they experienced through OSA. The forum allows for interactive dialogue between the students and the faculty of OSA to support the students construction of new knowledge. There are additional pedagogical strategies within the secure interface of OSA website. There is a repository of all the curriculum materials for the students to refer and use. The program assessment instruments can be administered, completed, and submitted online. Lastly, the student group projects can be uploaded, archived, and disseminated to the science community.

## Expandable and Sustainable

For OSA to make a significant impact on increasing the number of women in science, the program needs to be expandable and sustainable.

### *Expandability*

By expandable, this program model needs to be reproduced by other institutions across the nation to reach as many high school girls who are curious about science and who consider pursuing a career in science. As mentioned, OSA was initiated between NU and YWLCS in 2007. Within a year, two other Oncofertility Consortium institutions, University of California at San Diego and Oregon Health and Science University, created OSA programs. The Oncofertility National Science Education Network (ONSEN) was created to maintain communication, exchange of ideas, and consistency across the three OSA sites – OSA Chicago, OSA San Diego, and OSA Portland. To date, the total number of high school girls who have participated in OSA across the nation is 93 (47 OSA Chicago students, 30 OSA San Diego students, and 16 OSA Portland students). Northwestern University is working to develop an OSA starter kit to guide other Oncofertility Consortium institutions to easily implement the OSA program model.

According to the US Census of 2006–2007, there were approximately 8.3 million girls enrolled in high school [16]. Currently, with the three OSA sites, the program can only directly affect a total of 60 students per year from across the nation. The intention is to keep the size of the OSA student cohorts small in order to make a lasting impact on the students' lives. However, the Oncofertility Consortium is addressing how to include more high school girls by modifying and translating the OSA curriculum so that it can be integrated into an introductory or advanced high school biology curriculum. By basing the learning approach around oncofertility OSA teaches biological concepts traditionally covered in high school biology, such as cell structure and function, mitosis, meiosis, and DNA transcription and translation. If this oncofertility-based learning approach can be integrated into one school, a district, or a nationally recognized science curriculum, we will be able to maximize the number of students who have access to learning about the emerging field of oncofertility, and, by extension, inspire and prepare more girls to consider exploring the option of pursuing a career in science.

Each year OSA has been delivered, the visibility and popularity of the program within the NU community has increased and has intrigued other departments. Northwestern University's Institute for Women's Health Research, for example, is applying the OSA program model to other areas of science. In 2009, the OSA program model was used to develop and deliver the Cardiology Summer Academy in collaboration with the Bluhm's Cardiovascular Institute of Northwestern Memorial Hospital. Cardiology Summer Academy offered an intensive, 1-week program that focused on the field of cardiology and cardiovascular disease prevention. All of the same components of the OSA model were integrated into the development of the Cardiology Summer Academy but were condensed into a much shorter timeframe and offered in the summer. The Cardiology Summer Academy was a success and will be offered in 2010. In addition, two new OSA program-modeled academies will be initiated in 2010 – Infectious Disease Summer Academy and Physical Science Saturday Academy. Expanding the OSA program model to multiple areas of science will increase the total number of girls who are inspired and have access to resources that will guide them to make informed decisions about their educational and career trajectories.

## *Sustainability*

While the replication of the OSA model also contributes to its sustainability, short- and long-term evaluations of OSA are necessary to determine whether its goal of increasing the representation of women in science is being met. Currently, a variety of assessment tools are being administered and developed to measure the effectiveness and impact of OSA from multiple perspectives. Students, parents, and faculty of the OSA program are or will be subjects of both qualitative and quantitative research efforts. Conceptual learning, attitudinal, and behavioral changes are the general areas being studied to determine how the program directly affects the students. Assessment tools are being developed to measure parental involvement, influence, and attitudes toward their daughters' interests and pursuits in science, as well as the impact OSA has on the mentors, scientists, physicians, and other professionals who participate and deliver the OSA curriculum. To date, of the 47 students who have participated in OSA Chicago, 2 are college juniors, 16 are college sophomores, 15 are college freshman, and 14 are 12th graders in high school. Of the 33 who are in college, 27 (80%) are pursuing science-related majors.

The data collected is also used to demonstrate to external funders that OSA is a successful program that requires financial support in order to continue its efforts. Due to the socioeconomic status of the OSA Chicago population (80% of the students from YWLCS are on free and reduced lunch), the program has remained scholarship-based, annually receiving funding from NU and YWLCS to cover operating costs. However, this funding cannot be obtained for long term, thus necessitating the identification of a steady funding source. Financial support, therefore, is a critical element in the sustainability of OSA. The OSA faculty continue, year-after-year, to commit their time and efforts to sustain the program by collecting useful data and securing funding so as to inspire students to pursue their scientific inclinations.

## Conclusion

In summary, the Oncofertility Consortium has created a program model that is aggressively addressing the underrepresentation of women in science by expanding the translational science paradigm and implementing interventions that can immediately be put into action. The Oncofertility Consortium challenges the science community to rethink the traditional view of translational science by adding the "desk" to the paradigm, thus transforming the translational science paradigm into the "desk" to the "bench" to the "bedside." OSA created four practices to combat the T0 roadblock that exists between the "desk" and careers in science and causes the attrition of girls during the transition period between high school and college. The four practices are (1) a high school–university science partnership; (2) authentic and relevant science learning modules; (3) science mentor and support network; and (4) a web-based science communication platform (Fig. 25.2). These practices have the potential to mitigate the T0 roadblock and result in a more diverse population of scientists in the workforce. The expectation is that the OSA program model will increase the representation of women and minority scientists and in turn will increase the pace of translational science between the "bench" and the "bed."

The high school–university science partnership of OSA provides a portal for the high school girls to be exposed to state-of-the-art research and medical facilities at NU while working alongside faculty, 75% of whom are women. The science partnership highly depends on the involvement of the high school science teachers because of their daily interactions and relationships with the students. In return, the high school science teachers gain access to current scientific research and advancements and the opportunity to interact with working scientists to develop both their subject matter and pedagogical content knowledge. This professional development increases the high school teachers' capacity to improve and enhance their science curriculum that is offered to all their students back at school. Together the high school–university partnership creates a continuum that benefits the students, the educators, and the scientists.

OSA builds a synergistic science support network to foster more high school girls' interest and pursuits in science during the transition period between high school and college. Interactions among the high school girls, alumni of the program, high school science teachers, parents and family members, female medical students, scientists, and clinicians are highly encouraged throughout OSA. The relationship-building efforts with the high school girls do not end when the students graduate from high school but continue as they proceed into college. To support and strengthen the communication element of OSA, especially with the OSA alumni who move across the nation to attend college, an OSA website with communication functionalities has been constructed.

In conclusion, adding the "desk" domain completes the translational science paradigm. We argue that education is not only important to the next generation of careerists in science and medicine, it is critically important to the development of an educated public who can sift through information and advocate with more authority on behalf of their own health and welfare. The need for the scientific community to communicate the importance and relevance of scientific and medical research to the public has never been greater. Critical issues, including global warming, genetic testing, and stem cell research, affect us all on both personal and political levels. Yet studies show that the American public, though interested in science, maintains a relatively low level of scientific literacy, not only with regard to scientific facts but also in a clear understanding of the process by which scientific theories are tested, validated, and developed into tomorrow's breakthroughs. Furthermore, patients find it hard to make informed decisions if they are unfamiliar with mathematical principles such as percentages and risk calculations, which are commonly used to describe scientific and medical research findings. It is particularly important that advances in reproductive science and medicine be communicated in a clear way. We expect that the education of high school students within OSA and other modeled programs will contribute to the scientific careerist pipeline and generate a population of young people who are better enabled to understand the role of science in society, formulate their own opinions about research outcomes that are presented as controversial, and become better consumers of their health-care system. We predict that the students who are provided with the resources and experiences to achieve academic excellence at the "desk," over time, will stem the tide of scientific illiteracy by becoming better educated consumers as well as a contributors to the next generation of health-care advances.

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# Chapter 26
# MyOncofertility.org: A Web-Based Patient Education Resource Supporting Decision Making Under Severe Emotional and Cognitive Overload

**Kemi Jona and Adam Gerber**

> *Kristin, a 38-year-old female with breast cancer, was scheduled to begin treatment a week after receiving her diagnosis. Although she was in a four-year-long relationship, she had never thought about having kids. Kristin was told that embryo banking (IVF) was the best option for fertility preservation, and she had to decide immediately if she wanted biological children in order to start an egg-retrieval cycle. Because no other options were provided and she was uncertain about freezing embryos with her current partner, she ended up foregoing fertility preservation prior to the treatments that ultimately left her infertile.*
>
> *Ethan, a 19-year-old male, was in the hospital for four days awaiting surgery to remove a pelvic sarcoma. The surgery required removal of his testes rendering him infertile. During those four days, no one talked to him or his family about sperm banking, even though it could have been accomplished in a matter of minutes.*

## Introduction

As these scenarios illustrate, cancer patients and their families face a crucible of high-stake decisions during a time of extreme stress. They must cope with the shock and fear that attends a cancer diagnosis and navigate a complex set of treatment options. Then there is the often neglected issue of fertility preservation (FP) for those of reproductive age. Many cancer treatments, including surgery, radiation, and chemotherapy, carry significant risks of irreversibly compromising a patient's fertility. Patients are often unaware of these risks and in far too many cases, their health-care providers (HCPs) do not adequately inform them of these risks or available fertility preserving or sparing options.

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Improving both patient and provider education on the impact of cancer treatments on fertility and the wide range of available fertility options is essential to providing both quality and ethical health care. How can we create a resource that is accessible and effective during the very short and extremely stressful window of time between receiving a cancer diagnosis and commencing treatments that may have permanent and irreversible impacts on fertility? How can we provide the information that patients require to advocate for their needs and make informed decisions when they are already overwhelmed with highly technical medical information concerning their cancer diagnosis, treatment options, side effects, and likely prognosis?

In this chapter, we describe our efforts to address this unique patient education challenge through the design of an innovative web site called MyOncofertility.org. MyOncofertility.org educates health-care providers, patients, and patients' families about fertility preservation (FP) options when faced with a cancer diagnosis and subsequent treatment. MyOncofertility.org was designed to support patient education and time-critical decision making during periods of extremely high stress and information overload. We begin this chapter by looking at the advantages of the Internet as a tool for patient education in general. Then we focus on the specific challenges associated with patient education for oncofertility. Next, we identify design guidelines and explain how we used them to design the MyOncofertility.org site to address these challenges. Finally, we discuss how the lessons learned from the MyOncofertility.org project can be applied to the wider patient education context.

## The Internet as a Powerful Tool for Patient Education

Patient education has become a high priority in various preventative health care and disease management campaigns. Better-educated patients tend to be healthier and more compliant with prescribed treatment and medication regimens [1]. Patient education is a naturally interactive process and the Internet is a well-adapted medium for interactive learning. Furthermore, the advent of widely available Internet access and rich media has created exceptional opportunities for delivering high-quality patient education [2].

Much of the research in patient education has focused on the message content and not the specific affordances of the Internet for message delivery. As a learning tool, the Internet has some unique advantages over other media, including customization of information presented, 24/7 availability, worldwide distribution, a private learning environment, support for decision-making processes, the potential to simulate real-life experiences, easily updated content, and the presentation of rich media including videos and animations. A review of the literature is provided by Lewis [3]. A summary of this literature shows that clinical outcomes are improved, and that patients learn and retain information better when using computer-based media versus traditional instruction [3]. Lewis concludes, "The social integration and sharing of knowledge that occurs through these new connections may increase involvement in learning and expand patients' understanding of their medical conditions [3]."

Another important function of an Internet-based patient education site is that it allows HCPs to refer patients to such resources when appropriate, thereby freeing up time during office visits to focus on critical patient interactions such as diagnosis and discussion of treatment options and specific questions within their areas of expertise.

## Fertility Preservation and Patient Education

Fertility preservation in the face of a cancer diagnosis is fraught with challenges that must be thoughtfully considered when designing a suitable patient education resource. News of a cancer diagnosis can be traumatic, overwhelming, and imposes extreme stress and hardship on patients and their families. Yet it is essential that fertility preservation options be addressed prior to cancer treatment in order to provide patients with the greatest number of options and chances for fertility success [4–6].

The data on current practices in FP education and counseling are sobering. Research shows that women who are treated with either radiation or chemotherapy during reproductive years have a 40–80% chance of losing fertility [6]. With male patients, the sterility rate is slightly lower (30–75%), but nevertheless significant enough to merit FP counseling [7]. A study by Quinn et al. states that less than 50% of adult cancer patients of childbearing age "... receive adequate or appropriate education, counseling, and resources about reproductive decisions prior to their cancer treatment and at least 40% of cancer patients of childbearing age who receive treatment are not informed about the potential impact of treatment on fertility [8]." Furthermore, follow-up surveys demonstrate that cancer survivors with treatment-induced infertility are at greater risk for emotional distress [8]. While awareness of the importance of FP counseling is improving among HCPs, we know that we still have a long way to go.

## Fertility Preservation Communication Barriers and Challenges

Numerous barriers inhibit FP communication among health-care providers, patients, and their families. Given that early intervention is a critical success factor for surviving cancer, patients, patients' relatives, and HCPs are understandably anxious to start treatment as soon as possible. The urgency for cancer treatment upon diagnosis means that FP discussions are often neglected. Even when fertility options are discussed, the window for considering such options after an initial diagnosis is short and patients must be prepared to make well-informed, potentially life-changing decisions within a relatively short time horizon. In aggressive cancer cases, any unreasonable delays to treatment are strongly discouraged. Furthermore, there are significant costs associated with FP, particularly cryopreservation, which may require an out-of-pocket storage fee that can run from hundreds to thousands of dollars annually. Therefore, some HCPs and oncology social workers expressly neglect to discuss FP with cancer patients who clearly cannot afford it, citing ethical dilemmas in offering their patients a service the patient presumably cannot afford. Other patient characteristics, particularly patient age, number of children, and the stage of cancer development also influence HCPs in making unilateral decisions about discussing FP options with patients [9].

Although general guidelines by the American Society of Clinical Oncology (ASCO) have been established concerning FP [10], these guidelines are seldom referred to and not widely disseminated. While information resources concerning FP exist, many HCPs are simply unaware of such resources and do not provide them to patients. Furthermore, many oncologists believe that FP counseling is beyond the scope of their practice, and so they may be reluctant to discuss FP with patients; they may simply assume that other HCPs such as reproductive endocrinologists or obstetrician and gynecological surgeons will attend to this task. Ambiguity regarding the roles and responsibilities of HCPs with respect to FP often results in inadequate FP counseling or in some cases, no counseling [8, 9].

Lastly, the news of a potentially life-threatening cancer diagnosis is traumatic and can significantly impair a patient's, parents', or partner's decision-making abilities [11]. Given the wide range of treatment options and the large volume of medical information on oncology, patients are often overwhelmed with treatment options and unable to process yet another major medical decision such as FP. The urgency, stress, and confusion associated with a cancer diagnosis, the lack of patient education about the impact of cancer treatments on fertility options, and HCPs who often neglect to raise the issue with patients or are not up to date on the full range of FP options all combine to make patient education on FP both difficult and essential.

The medical and social science literature are unambiguous about the need for better fertility preservation education for patients of cancer. We now turn to an exploration about how the MyOncofertility.org web site was designed to meet the challenges of designing a patient education resource for oncofertility.

## MyOncofertility.org Design Goals

Cancer and oncofertility are serious subjects. Nevertheless, MyOncofertility.org provides a hopeful, human, and inspirational message to users in a way that is both respectful and authoritative. The following are the goals that guided the design of MyOncofertility.org and a discussion of the various methods employed to achieve these goals (Table 26.1).

### *The Use of Media*

MyOncofertility.org makes use of several media, including video, animations, still images, and text. Expert videos and video testimonials of survivors as well as those of relatives, partners, and parents of cancer patients are a prominent feature of the

**Table 26.1** Principal goals for MyOncofertility.org

| Principal goals for MyOncofertility.org |
|---|
| A. Create a resource for patients, their parents, and partners that is accessible and effective during the very short and extremely stressful window of time between receiving a cancer diagnosis and commencing treatments that may have permanent and irreversible impacts on fertility |
| B. Provide the information that patients require to advocate for their needs and make informed decisions |
| C. Help alleviate/mitigate feelings of information overload and stress; do not contribute to information overload |
| D. Empower users to be in control of the quantity, complexity, pace, and type of information presented |
| E. Help users identify with others in similar situations to assuage feelings of isolation |

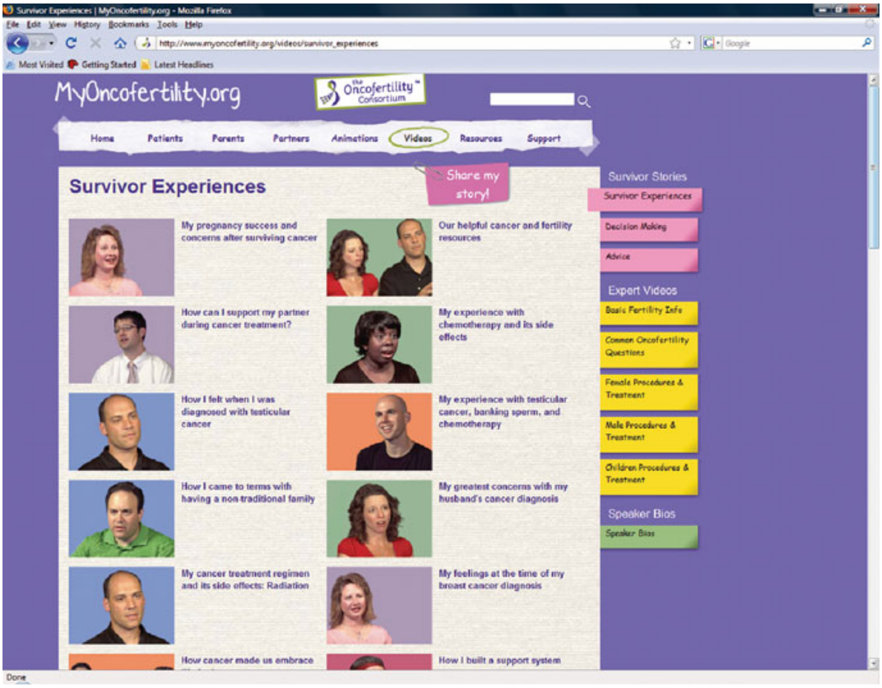
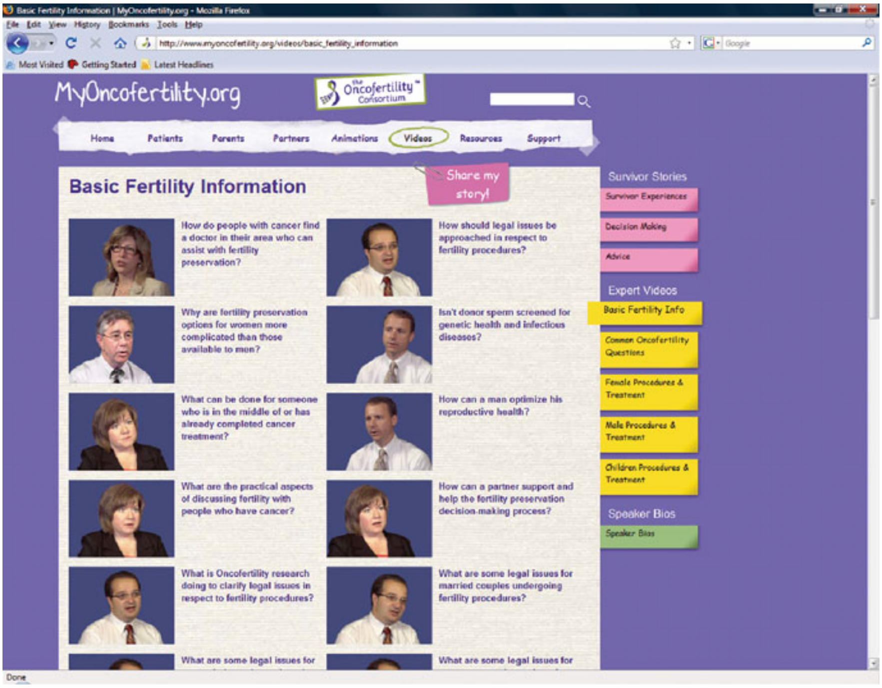


**Fig. 26.1** MyOncofertility.org videos of survivor experiences

site (see Figs. 26.1 and 26.2). Research in the field of narratology has confirmed that storytelling plays a privileged role in human communication. Postmodern theorist Richard Rorty suggests that the principal role of narrative is that it fosters human solidarity by creating shared experiences [12]. The use of video supports one of the major goals of the site, which is to help users identify with others in similar situations in order to alleviate their feelings of isolation. Video is also particularly useful for children, the elderly, patients with poor literacy, or those with impaired vision.



Basic Fertility Information

How do people with cancer find a doctor in their area who can assist with fertility preservation?

How should legal issues be approached in respect to fertility procedures?

Why are fertility preservation options for women more complicated than those available to men?

Isn't donor sperm screened for genetic health and infectious diseases?

What can be done for someone who is in the middle of or has already completed cancer treatment?

How can a man optimize his reproductive health?

What are the practical aspects of discussing fertility with people who have cancer?

How can a partner support and help the fertility preservation decision-making process?

What is Oncofertility research doing to clarify legal issues in respect to fertility procedures?

What are some legal issues for married couples undergoing fertility procedures?

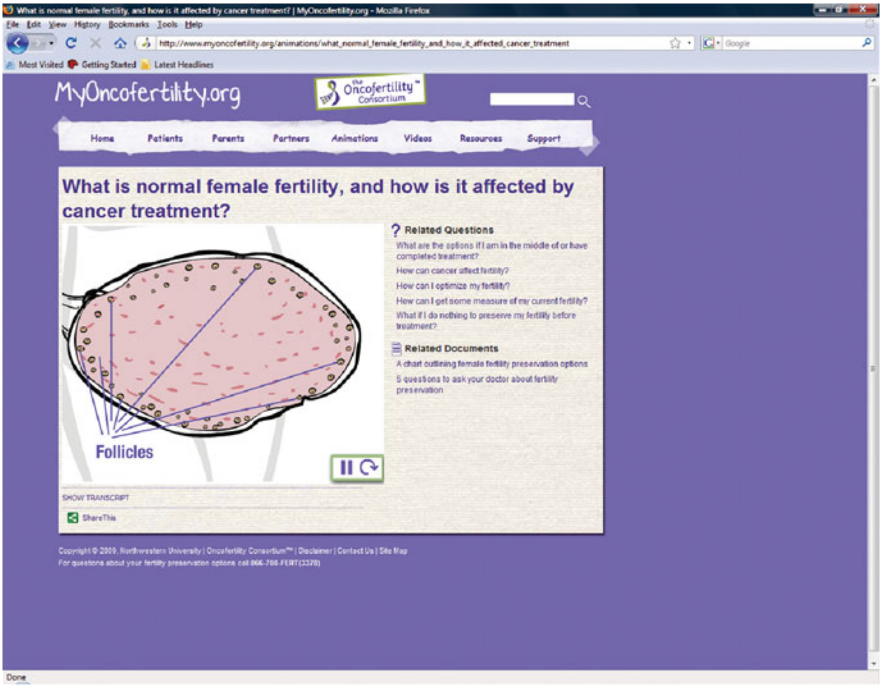
What are some legal issues for

What are some legal issues for

**Fig. 26.2** MyOncofertility.org videos of experts

Studies have shown that video provides patients with "opportunities for enhanced social interaction, diminished feelings of isolation, and improved self-esteem [3]." A study comparing various forms of patient education media found that patients were able to "accomplish learning tasks significantly better when using interactive video [13]." The same study demonstrated that patients with poor literacy can benefit from the customized pace of video instruction and the non-threatening, private learning environment. Another study found that interactive video is preferred to text among patients [14]. Video was critical in achieving the design and usability goals for the MyOncofertility.org web site. While video is more expensive to produce than textual content, we believe the benefits far outweigh the costs.

Narrated animations (see Fig. 26.3) were used to illustrate various fertility preservation procedures and educate users about how cancer treatments affect fertility. Animations were developed to convey complex, multi-step processes using a combination of auditory narrative and animated visuals. Though the processes described by the animations are complex, the animations themselves are purposefully uncomplicated, void of any superfluous visual information, and describe oncofertility processes in concise language that is easy for a lay audience to understand. Analysis of usage data indicates that visitors find these rich media resources among the most valuable on the site (see full discussion below).



What is normal female fertility, and how is it affected by cancer treatment? | MyOncofertility.org - Mozilla Firefox

http://www.myoncofertility.org/animations/what_normal_female_fertility_and_how_it_affected_cancer_treatment

What is normal female fertility, and how is it affected by cancer treatment?

? Related Questions

What are the options if I am in the middle of or have completed treatment?

How can cancer affect fertility?

How can I optimize my fertility?

How can I get some measure of my current fertility?

What if I do nothing to preserve my fertility before treatment?

Related Documents

A chart outlining female fertility preservation options

5 questions to ask your doctor about fertility preservation

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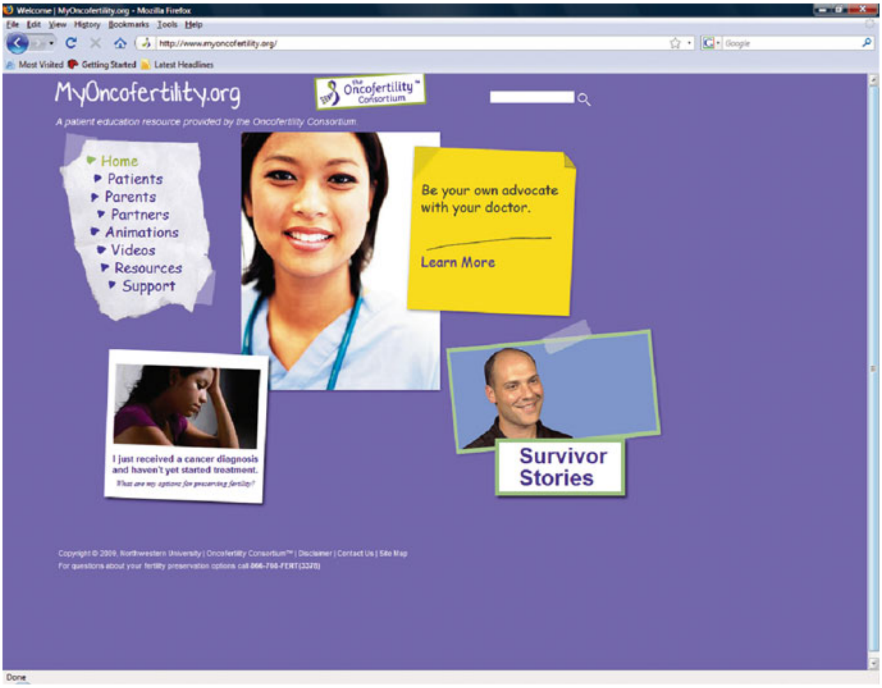
For questions about your fertility preservation options call 866-708-FERT(3378)

**Fig. 26.3** MyOncofertility.org animation of normal female fertility

## *An Appropriate Design Motif*

A key goal of our interface design for the MyOncofertility.org site was to make it feel warm, welcoming, accessible, and non-threatening to our audience. We decided to adopt a scrapbook motif as an informal, yet dynamic approach to achieve this design goal. The scrapbook motif was achieved by employing various scrapbook design elements and frames such as post-it notes, polaroid photos, torn paper, paper-clips, and Scotch tape (see Fig. 26.4). In order to soften the interface, the site employs hand-drawn elements and scripted, sans-serif fonts. The animations used within the site were also hand-drawn as opposed to machine rendered. These hand-drawn elements create a more human and less threatening interface (see Figs. 26.4 and 26.3). The use of warm pastel colors throughout the site is reminiscent of a pre-school or perhaps a maternity ward and thus provides hope to cancer patients desiring biological children. Among the few exceptions to the pastel theme is the use of a deep blue background for expert videos. The consistent deep blue color conveys authority and consistency of message.

In designing the look and feel of the site, we chose to include photographs of individuals and families that our audience would relate to and that would emphasize our goals of making the site feel warm, welcoming, and non-threatening. The still



A patient education resource provided by the Oncofertility Consortium

Be your own advocate with your doctor.

I just received a cancer diagnosis and haven't yet started treatment.

*What are my options for preserving fertility?*

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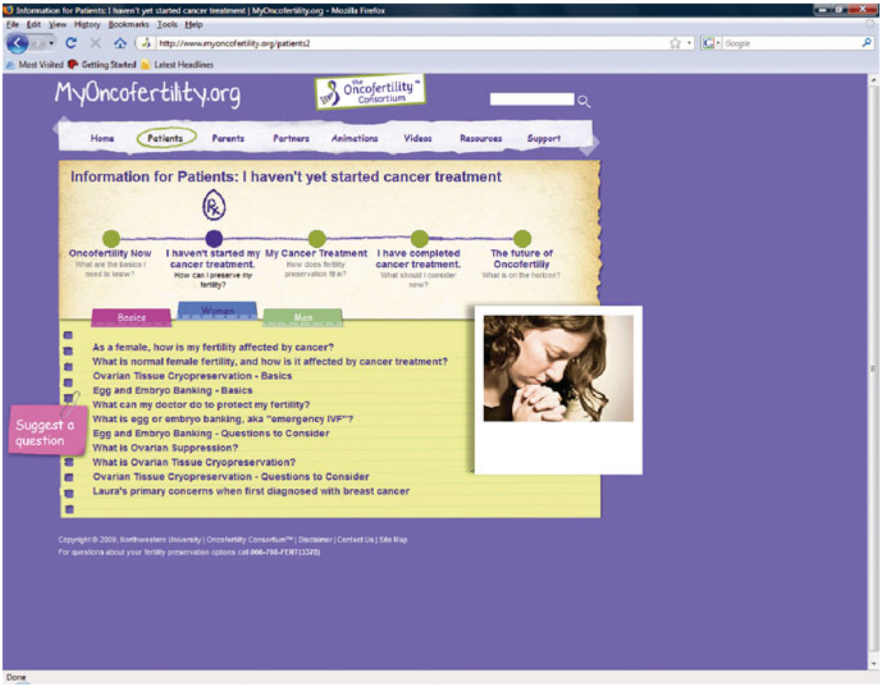
For questions about your fertility preservation options call 866-708-FERT(3378)

**Fig. 26.4** MyOncofertility.org home page

images used for the site were carefully selected and vetted by focus groups of cancer patients and their relatives in collaboration with Gilda's Club of Chicago (see Figs. 26.4, 26.5, and 26.6). For example, it was initially unclear as to whether using an image of a pregnant woman would be offensive to visitors who might be struggling with fertility issues. However, a series of focus group sessions demonstrated that such an image was not only inoffensive but also hopeful to prospective parents. In keeping with the genuine nature of the site, the images used within the site portray a wide range of human emotions without trying to whitewash the realities of cancer and fertility treatments.

## *User Control and Participation*

When users first enter the site, they are presented with an intuitive navigation scheme and are invited to self-identify as patients, parents, or partners (see Fig. 26.5). The information presented to them subsequent to this self-identification is filtered to be relevant to their specific needs. A secondary navigation scheme uses a treatment timeline to situate users at various stages – from initial diagnosis to survivorship – further filtering the relevant information presented to them.



Information for Patients: I haven't yet started cancer treatment

As a female, how is my fertility affected by cancer?
What is normal female fertility, and how is it affected by cancer treatment?
Ovarian Tissue Cryopreservation - Basics
Egg and Embryo Banking - Basics
What can my doctor do to protect my fertility?
What is egg or embryo banking, aka "emergency IVF"?
Egg and Embryo Banking - Questions to Consider
What is Ovarian Suppression?
What is Ovarian Tissue Cryopreservation?
Ovarian Tissue Cryopreservation - Questions to Consider
Laura's primary concerns when first diagnosed with breast cancer

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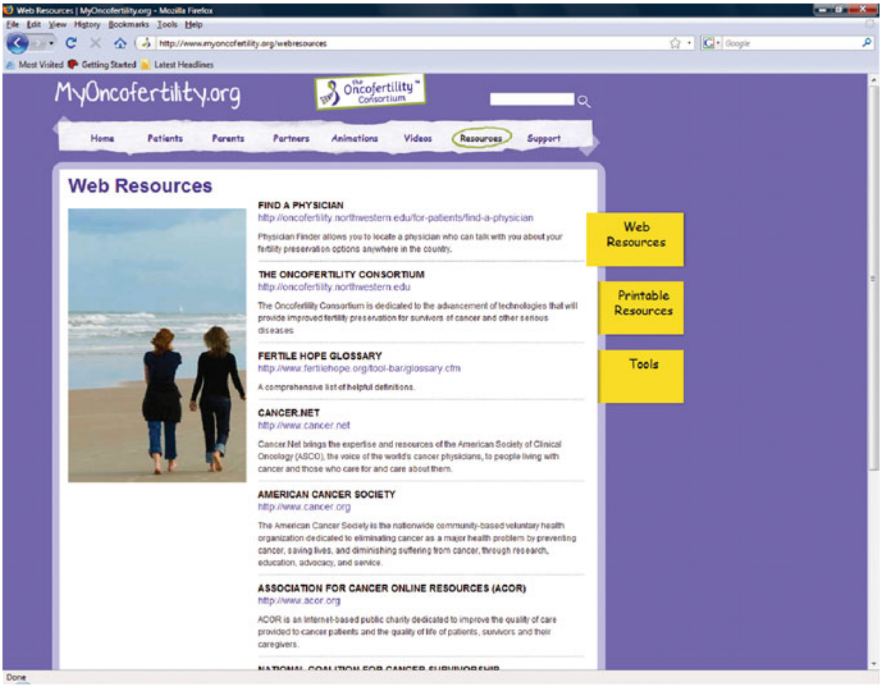
**Fig. 26.5** MyOncofertility.org patient timeline for women

Since information overload has been identified as one of the key barriers to FP communication, the site was designed for quick access to layered information which progresses in complexity as users drill down to greater and greater detail. In a similar fashion, the questions posed to users on side- and sub-panels progress from simple to complex.

Throughout the site, a question and answer (Q&A) model was employed based on the expert/novice dyad conversation model. Modeled after the Q&A dialogue that would occur between a doctor and a patient (or between teacher and student), users are presented with questions that, when clicked, link to an answer to that question. After reading or viewing the answer (as text, video, or animation), a number of related follow-up questions or resources are presented. By clicking on a follow-up question, the user mimics the natural question/answer/follow-up question process that occurs in face-to-face dialogues.

User participation is a critical aspect of the site both pre- and post-launch. Focus groups were consulted throughout the design phase and users are invited to participate and contribute to the site as it evolves. The scrapbook motif (see above) supports the site's dynamic, interactive, and evolving nature. Pink notes prompting users for feedback with captions such as "Suggest a question" or "Share my story!" give users the option to contribute to the site by sharing resources or a personal story of their experience with cancer and FP. Such an approach fosters a sense of solidarity



Web Resources

FIND A PHYSICIAN
http://oncofertility.northwestern.edu/for-patients/find-a-physician

Physician Finder allows you to locate a physician who can talk with you about your fertility preservation options anywhere in the country.

THE ONCOFERTILITY CONSORTIUM
http://oncofertility.northwestern.edu

The Oncofertility Consortium is dedicated to the advancement of technologies that will provide improved fertility preservation for survivors of cancer and other serious diseases

FERTILE HOPE GLOSSARY
http://www.fertilehope.org/tool-bar/glossary.cfm

A comprehensive list of helpful definitions.

CANCER.NET
http://www.cancer.net

Cancer.Net brings the expertise and resources of the American Society of Clinical Oncology (ASCO), the voice of the world's cancer physicians, to people living with cancer and those who care for and care about them.

AMERICAN CANCER SOCIETY
http://www.cancer.org

The American Cancer Society is the nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer, through research, education, advocacy, and service.

ASSOCIATION FOR CANCER ONLINE RESOURCES (ACOR)
http://www.acor.org

ACOR is an Internet-based public charity dedicated to improve the quality of care provided to cancer patients and the quality of life of patients, survivors and their caregivers.

NATIONAL COALITION FOR CANCER SURVIVORSHIP

**Fig. 26.6** MyOncofertility.org web resources

and community and allows us to be responsive to users' needs for information that may have been initially overlooked. Future plans for the site include creating an online community via message boards and social networking.

## Applying Design Principles from MyOncofertility.org to Other Patient Education Web Sites

To facilitate the application of the design of MyOncofertility.org to other patient education web sites, we now examine the key principles that informed the design of the site and the user interaction it supports. Table 26.2 summarizes these principles, which are then discussed in turn.

(1) *Users should be in full control of the browsing experience*. Among the most important principles for designing a patient education resource is that users should be in full control of the browsing experience. In the case of MyOncofertility.org, this meant providing an intuitive navigation bar either to the left (see Fig. 26.4) or on top of the page (see Fig. 26.5). All the videos and animations used within the site have navigation bars that allow users to stop, play, rewind, pause, or skip to any part as they chose. Furthermore, users are

**Table 26.2** Principles for designing a patient education resource

| Principles for designing a patient education resource |
|---|
| (1) Users should be in full control of the browsing experience and only receive information they request |
| (2) Limit the quantity of information provided at any given time and delimit to a single topic |
| (3) Limit complexity of information to depth that the user requests – start simple and allow for drill down |
| (4) Utilize a navigation scheme that provides a common and easily recognized framework for your audience |
| (5) Employ a Q&A model such as the one based on the expert/novice dyad conversation model |
| (6) Use video and animations strategically to help make complex concepts, processes, treatment effects, or timelines understandable and accessible |
| (7) Use the power of first-person video stories to improve communication of difficult topics, create emotional connections, and assuage patient feelings of isolation |
| (8) Make sure each page of the site can be found directly via search engines by using search engine-friendly HTML |

given the opportunity to read the transcripts of both videos and animations. No information is presented without the user initiating a request.

(2) *Limit the quantity of information provided at any given time and delimit to a single topic*. Information overload is often an issue with patient education, and this was certainly the case with oncofertility. Therefore, limiting the amount of information that users can access at any given time is crucial to providing good user experiences. MyOncofertilty.org invites users to self-identify as patients, parents, or partners. Upon self-identification, the information presented to users is specific to their particular case. Also, a navigational timeline situates users at a particular stage in their journey, further delimiting the information presented to them.

(3) *Limit complexity of information to depth that the user requests – start simple and allow for drill down*. In addition to the design features described above, MyOncofertility.org presents information in layers of complexity. Initial questions and answers are general and non-technical. Follow-up questions become increasingly more specific and technical; only after viewing the answer to a general question are the more detailed questions presented. This means that many of the resources on MyOncofertility.org are intentionally hidden from users until such time as they request them by drilling down, or by navigating to them from menus or timelines.

(4) *Utilize a navigation scheme that provides a common and easily recognized framework for your audience*. Employ chronology, roles, and user characteristics to develop an intuitive navigation scheme that meets the needs of your audience and does not force them to adopt technical classification schemes more familiar to experts (e.g., disease stages). Whenever relevant, the navigation scheme should be time sensitive and address your audience before, during, and after treatment. Consider roles (patient, parent, and provider) and user characteristics, such as age, gender, phase in treatment, or other treatment-specific

criteria as additional navigational structures to help users find the information most relevant to them.

(5) *Employ a Q&A model such as the one based on the expert/novice dyad conversation model.* The expert/novice dyad conversation model is among the most interactive models for learning and, furthermore, the Internet is particularly well suited to this model. We recommend modeling information access on a site after a question and answer dialogue which might occur between a health-care provider and a patient and then provide branching logic for follow-up questions.

(6) *Use video and animations strategically to help make complex concepts, processes, treatment effects, or timelines understandable and accessible.* Studies show the effectiveness of animations and videos in conveying complex processes such as those associated with medical treatment. Employing animations and videos throughout a patient education web site will make it more accessible.

(7) *Use the power of first-person video stories to improve communication of difficult topics, create emotional connections, and assuage patient feelings of isolation.* Studies have demonstrated that video is not only an effective learning tool but also has the additional benefit of alleviating feelings of isolation and anxiety among users. We recommend that patient education web sites make strategic use of both expert videos and survivor/relative testimonials.

(8) *Make sure each page of your site can be found directly via search engines by using search engine-friendly HTML.* When using video, Flash, or other rich media, provide full text transcriptions that are visible to search engines. Early prototypes of MyOncofertility.org made extensive use of a vector graphics rendering technology called Flash. Though Flash sites are among the most dynamic and interactive on the Internet, there is very little text which can be indexed within Flash sites, and so search engines often have difficulty navigating and indexing such sites as well as the links contained therein. Subsequent iterations of MyOncofertility.org used search engine-friendly HTML. All the videos and animations within MyOncofertility.org were accompanied by text transcriptions visible to search engines making them a simple click away from users (see Fig. 26.3). These transcriptions (see Table 26.2) proved to be extremely useful as they allowed search engines to properly index the content of both video and animations.

## Insights from MyOncofertility.org Usage Data

According to data gathered from Google Analytics for the period between October 26, 2008 and October 26, 2009, MyOncofertility.org had 10,754 visitors, of which 80% were new visitors. On average, users visited four pages and spent 3 min viewing the site per visit. A closer examination of usage patterns is also quite revealing.

A particularly useful measure in web site analytics is landing page data. A landing page is a web page that is linked directly from other sites, or one that visitors access directly from search engines (rather than arriving from other pages within

**Table 26.3** Top 10 landing pages (data compiled from Google analytics for the period between October 26, 2008 and October 26, 2009)

| Top 10 landing pages | Page visits (annual) |
|---|---|
| Home page | 4,408 |
| Video (expert): what_cost_freezing_eggs_and_embryos | 221 |
| Video (survivor): i_was_diagnosed_stage_2_hodgkins_lymphoma_during_my_engagement | 208 |
| Video (survivor): my_experience_deciding_use_donor_sperm_my_family | 187 |
| Video (expert): what_difference_between_icsi_and_ivf | 155 |
| Animation: what_normal_female_fertility_and_how_it_affected_cancer_treatment | 141 |
| Video (survivor): my_experience_chemotherapy_and_its_side_effects | 120 |
| Video (expert): pregnancy_safe_after_chemotherapy | 115 |
| Video (survivor): how_i_learned_inject_myself_ivf_process | 106 |
| Video (expert): who_dr_teresa_woodruff | 105 |

the site itself). Validating our use of rich media like video and animation on the site, Table 26.3 below shows that the top landing pages – aside from the home page – were either video or animation pages. These data confirm three important observations: (1) third parties appreciate the value of the videos and animations on MyOncofertility.org because they are placing direct links to them on their own web sites; (2) search engines are properly indexing the transcribed text content for videos and animations at MyOncofertility.org so that they can be easily found; and (3) these pages contain among the most highly relevant information for popular search terms sought by our visitors.

Among the greatest strengths of using the Internet over other media is worldwide exposure. Table 26.4 lists the top 10 countries accessing the MyOncofertility.org web site. Not surprisingly, not only English-speaking countries but also countries where English is widely spoken as a second language were well represented among users. Other factors that may have contributed to these data are active oncofertility researcher communities within particular regions, oncofertility events hosted

**Table 26.4** Top 10 user countries (data compiled from Google analytics for the period between October 26, 2008 and October 26, 2009)

| Top 10 user countries | Visits (annual) |
|---|---|
| United States of America | 8,001 |
| United Kingdom | 483 |
| Canada | 390 |
| Australia | 223 |
| India | 214 |
| Netherlands | 177 |
| Philippines | 78 |
| Germany | 55 |
| Poland | 54 |
| Ireland | 53 |

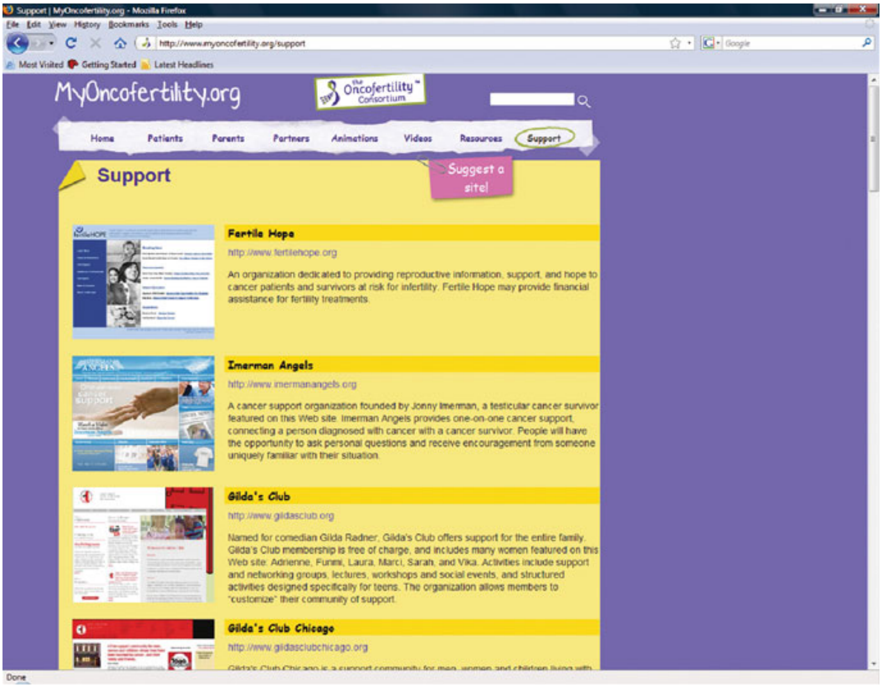
by particular countries, and articles on oncofertility published in journals that are popular in particular regions. An analysis of the country of origin for visitors to the site can indicate which languages would be top priority for any translation of the site.

The primary way that a web site is found by potential visitors is through search engines like Google or Yahoo!. Analyzing the search terms used most frequently by visitors arriving to the site from search engines is revealing because such terms indicate preferences and trends among users. These data can then guide the authoring of content for the site in subsequent iterations so that popular search terms appear and thus attract visitors to those pages. The following table shows the top 20 keyword searches for MyOncofertility.org. The keyword phrases that stand out are “Teresa woodruff,” “adriomyacin,” “oncofertility consortium,” “cost of freezing eggs,” “difference between icsi and ivf,” “pregnancy after chemotherapy,” and “fertility hotline.” Teresa Woodruff founded the oncofertility consortium and coined the term oncofertility – thus it makes sense that visitors might use her name or that of the consortium to find the site. The other keyword phrases are technical, reflect user concerns about the costs associated with fertility preservation, or are terms one might use to seek help (Table 26.5).

After search engines, the other way that visitors can find this site is by following links to it posted on other sites they are reading or browsing. These are called referring sites, and there are a total of 563 such sites that currently point to pages on MyOncofertility.org. In addition to directing visitors to a site, having many referring sites – and especially highly ranked ones – are important because this directly impacts how highly search engines rank a site. Being ranked at or near the top

**Table 26.5** Top 20 keyword search terms (data compiled from Google analytics for the period between October 26, 2008 and October 26, 2009)

| Top 20 keyword search terms | Visits per keyword search term (annual) |
|---|---|
| My oncofertility | 161 |
| Oncofertility | 120 |
| Myoncofertility | 102 |
| Myoncofertility.org | 88 |
| Teresa woodruff | 64 |
| Adriomyacin | 53 |
| Oncofertility consortium | 46 |
| Cost of freezing eggs | 41 |
| Difference between icsi and ivf | 35 |
| Cost of freezing embryos | 34 |
| Stage 2 lymphoma | 33 |
| Wet heat | 33 |
| Difference between ivf and icsi | 30 |
| Pregnancy after chemotherapy | 29 |
| Myoncofertility.com | 28 |
| www.myoncofertility.org | 27 |
| Female procedures | 26 |
| Fertility hotline | 26 |
| Stage 2 hodgkins lymphoma | 26 |
| Embryo banking | 25 |



Support

**Fertile Hope**

http://www.fertilehope.org

An organization dedicated to providing reproductive information, support, and hope to cancer patients and survivors at risk for infertility. Fertile Hope may provide financial assistance for fertility treatments.

**Imerman Angels**

http://www.imermanangels.org

A cancer support organization founded by Jonny Imerman, a testicular cancer survivor featured on this Web site. Imerman Angels provides one-on-one cancer support, connecting a person diagnosed with cancer with a cancer survivor. People will have the opportunity to ask personal questions and receive encouragement from someone uniquely familiar with their situation.

**Gilda's Club**

http://www.gildasclub.org

Named for comedian Gilda Radner, Gilda's Club offers support for the entire family. Gilda's Club membership is free of charge, and includes many women featured on this Web site: Adrienne, Funmi, Laura, Marci, Sarah, and Vika. Activities include support and networking groups, lectures, workshops and social events, and structured activities designed specifically for teens. The organization allows members to "customize" their community of support.

**Gilda's Club Chicago**

http://www.gildasclubchicago.org

Gilda's Club Chicago is a support community for men, women and children living with

**Fig. 26.7** MyOncofertility.org support groups

of search engine results means that it is much more likely that visitors will find your site when they search for a particular word or phrase (since most of us do not bother scanning past the first page of search results!). The table below lists the top referring sites to MyOncofertility.org. The top referring sites are associated with Northwestern University, a major center for oncofertility research, while others are patient resource sites. Publicity such as a *New York Times* article has also driven traffic to the site (Table 26.6).

**Table 26.6** Top 10 referring sites (data compiled from Google analytics for the period between October 26, 2008 and October 26, 2009)

| Top 10 referring sites | Type of site | Visits directed from referring site (annual) |
|---|---|---|
| Oncofertility.northwestern.edu | Academic | 515 |
| Nlm.nih.gov | Government | 264 |
| Nytimes.com | News | 157 |
| Cancer.northwestern.edu | Academic | 85 |
| Northwestern.edu | Academic | 60 |
| Mskcc.org | Hospital | 39 |
| Google.com | Search engine | 35 |
| Cancervive.org | Cancer advocacy | 31 |
| Nmh.org | Hospital | 30 |
| Youngsurvival.org | Cancer advocacy | 30 |

## Conclusion

MyOncofertility.org is a patient education resource that addresses an important yet underserved patient community. MyOncofertility.org went through several design iterations as we adapted to feedback and issues in the user community. Furthermore, MyOncofertility.org is a dynamic project that keeps evolving to keep pace with Internet technology and user needs. Our goal in writing this chapter was to share the lessons learned from the MyOncofertility.org development experience with others charged with developing similar patient education resources. We hope that readers will have a much better appreciation for the issues related to patient education, and that the design principles above will serve as useful guidelines for those in a position to design patient education web sites in the future.

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# Chapter 27

# Anticipating Ovarian Tissue Cryopreservation in the Health-Care Marketplace: A Willingness to Pay Assessment

**Shauna L. Gardino, Andrew Sfekas, and David Dranove**

## Introduction

Advances in cancer therapy are allowing patients to live longer, healthier lives, changing the landscape of survivorship, and opportunities for life after disease. These cancer therapies, though, are not without consequences: more cancer patients are burdened with the long-term side effects of aggressive cancer therapies. An important example is the impact of radiation and chemotherapy on male and female fertility. The term oncofertility refers to developing scholarship on the issues of fertility management arising from oncology therapy, combining the two diverse fields of oncology and fertility into one unified discipline.[1] Oncofertility researchers are actively working to develop fertility preservation options for the unique population of cancer patients and bringing these options to the patient's bedside as they become available.

A new oncofertility procedure, ovarian tissue cryopreservation (OC), provides an alternative to female cancer patients for whom embryo or egg banking is not a viable option. Although this technique is still considered experimental, researchers are hoping it can fill the current gap in options for female patients. The science behind OC is actively being studied in the laboratory, but little is known about the real-world implications of this medical procedure, including whether patients would pay for it and what level of value they would place on it. The purpose of this study is to directly assess whether young women facing the prospects of cancer treatment would value fertility preservation and, if so, by how much.

To assess the relative economic value of fertility, we administer a "willingness to pay" (WTP) survey in which we ask respondents how much they would be willing to pay for the OC procedure, for treatment for other health problems, and for a variety of consumer goods and services. We then compare their WTP for OC to

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[1] The term oncofertility was coined by Dr. Teresa Woodruff at Northwestern University's Feinberg School of Medicine.

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their WTP for goods and services that are already commonly available, drawing comparisons between the two groups. Through this assessment, we seek to answer the following two questions: "What is fertility preservation worth?" and "What are the characteristics of individuals who most highly value fertility preservation?"

Because OC is likely to be costly, many individuals will not have the financial wherewithal to pay for this medical procedure. Thus, a critical question is whether they would be willing to pay for insurance to cover the cost of the procedure. Our survey concludes by asking respondents about their WTP for OC insurance coverage, allowing our analysis to fully address the prominent questions related to how this technology will operate in the health-care marketplace.

## Fertility Preservation Options

Radiation and chemotherapy as part of aggressive cancer treatment regimes can destroy a woman's fertility, causing her to undergo early menopause or even lose her fertility completely. There are a number of existing fertility preservation procedures available to female cancer patients, the most well established being embryo and egg banking. In both procedures, eggs are harvested from a woman and frozen for later use with in vitro fertilization.[2] These two options, however, entail their own list of complications and are not available to every patient. There are two major classes of patients for whom these are not viable options: prepubescent women and women whose cancer therapy must begin immediately (e.g., women diagnosed with leukemia). Embryo and egg banking require a 2- to 3-week delay in cancer treatment, so they are not an option if therapy must begin immediately. Every year, between 1,600 and 1,700 women and girls under the age of 30 in the United States are diagnosed with cancer and are at risk for losing their fertility. There is also an unknown number of women who may avoid embryo and egg banking due to the side effects of egg harvesting and the IVF procedure.

Ovarian tissue cryopreservation is an experimental procedure designed for women who are not candidates for or do not choose to pursue embryo or egg banking. Patients opting for OC will undergo a surgery to remove one whole ovary prior to cancer treatment. Tissue from the resulting ovary is then frozen and preserved at a cryogenic facility for use at a later date. Subsequent to cancer treatment (or at a later date when the woman wants to pursue a pregnancy), researchers thaw the ovarian tissue and attempt to mature the follicles from the tissue within the laboratory. The mature oocyte is then fertilized, either with a partner's sperm or with a donor's sperm, and the resulting embryo is transferred back into the woman using IVF.

Ovarian tissue cryopreservation offers numerous benefits when compared to the prevailing treatment options. First, OC can be performed on prepubescent female

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[2] In embryo banking, the harvested eggs are fertilized with a partner's or donor's sperm and the resulting embryo is frozen for later use with IVF.

patients who cannot undergo hormone treatment and otherwise have no other fertility treatment options.[3] Second, the procedure can be performed immediately, delaying cancer treatment for at most 1–2 days, while the hormone therapies required for embryo and egg banking can entail an average delay of 2–3 weeks. Third, OC provides a viable fertility option for women who wish to avoid any side effects associated with hormone treatments. Finally, since OC does not require immediate fertilization of an egg, it allows women who do not have a partner or access to donor sperm more control over with whom to have biological children than they would have with embryo banking.

## Willingness to Pay

OC can be a costly technology. For the 43 OC procedures performed to date, the average facility charge has been approximately $30,000, although the range of actual costs is quite varied. For example, Northwestern University has negotiated a fixed rate of $12,000 per procedure, and a number of other medical centers have package prices available for women choosing to undergo OC. Another factor to consider in estimating the actual cost is insurance coverage. To date, the majority of OC procedures have been covered by health insurance companies; indeed, all patients with health insurance who have undergone OC at Northwestern have received insurance coverage for the procedure (Gerrity, 2009, Executive Director of the Oncofertility Consortium, Personal conversation). However, as only 43 procedures have been performed to date, these statistics are still preliminary. Due to the varied institutional prices and insurance status of cancer patients, it is difficult to estimate the actual costs of OC. A useful comparison, however, can be made between OC and IVF to gauge the social value of OC. The average cost of IVF is $12,400 and insurance companies generally cover 40–50% of this cost. Society has clearly indicated that the benefits of IVF exceed the cost, as evidenced by the widespread use of the procedure and insurance coverage. Whether the benefits of OC exceed its much higher cost, however, remains unclear. The actual cost of the OC procedure as well as its relative social value will become more apparent as the procedure becomes more widespread.

One way to assess the value of OC would be to perform a cost-effectiveness analysis, for example, by measuring QALYs (quality-adjusted life year) gained per dollar spent. There is no consensus about how to value fertility in QALYs, however [1–3]. The fact that the patient would be dealing with cancer therapy and an uncertain prognosis further complicates using the QALY approach to assess the value of the OC procedure.

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[3] Though removal of ovarian tissue is an established procedure, the techniques for freezing and thawing the tissue and use of the thawed tissue in “in follicle maturation” (IFM) are still experimental and this procedure has not yet resulted in pregnancy in humans. (http://www.myoncofertility.org/articles/what_oncofertility_consortiums_current_project)

Rather than rely on cost-effectiveness analysis (CEA), we can instead perform a cost–benefit analysis, in which both costs and benefits are denominated in dollars. As per the previous discussion, we have already completed a preliminary analysis of the cost of OC. The main purpose of this study is to explore the benefits of the OC procedure. One such way to dollar denominate the benefits of a good or service is to examine the price that consumers pay in the current market place. By definition, those consumers who purchase the product have a WTP that exceeds the price. This approach, however, is not practical for services like OC where consumers are still learning about the value and the price is substantially subsidized.

Contingent valuation (CV) surveys – essentially, asking people how much they would pay – are a necessary substitute when market prices are not appropriate measures of WTP. CV has long since been used to determine the value of nonmarket goods and services. CV surveys use a series of questions asking respondents how they would assess the value of a technology or procedure based on the respondents' own personal experiences. In this approach, survey design is critical to obtaining meaningful WTP estimates [4]. The surveyor must thoroughly describe the attributes of the good or service and should also encourage the respondent to think about valuation of a variety of other goods and services. When probabilities are involved (such as procedures like OC that may have less than a 100% success rate), respondents should be made comfortable thinking about probabilities in general (e.g., the probability of changing jobs within the next year). In designing our CV survey for OC we were careful to include all of these considerations in our survey design. Since we interviewed both young women and parents with young daughters, we adjusted the wording of certain questions to reflect the differences between these two groups. This analysis focuses only on the responses of the cohort of young women, as the parent interviews are not yet completed.

Existing research utilizing the CV methodology to assess the value of infertility procedures demonstrates the appropriateness of this approach in the realm of reproductive health. Neumann and Johannesson (1994) have previously implemented a CV survey to estimate the WTP for the IVF procedure itself and for insurance coverage for IVF [1]. They report an average WTP of about $25,760 (in 2009 dollars; $17,730 in 1994 dollars) for IVF treatment that has a 10% success rate. They also report a WTP of $865 for a lifetime insurance benefit to cover the costs of IVF with a similar 10% success rate. In 2002, 0.3% of women required the use of IVF, which would work out to an actuarially equivalent payment of $77 for each IVF procedure. These estimates demonstrate the applicability of CV surveys and the WTP approach in understanding and estimating the relative value of fertility procedures and insurance coverage for these same procedures.

## Survey Methods

In order to estimate the anticipated value of OC in the health-care marketplace, we conducted a contingent valuation survey. We administered surveys to two different groups: (a) young women (ages 18–25) and (b) parents (ages 20–69) with daughters (ages 5–17). The survey begins with basic demographic questions, including family history and religious preferences. After hearing a detailed description of the OC procedure, respondents are asked to imagine that they (or their daughter) have recently been diagnosed with leukemia and require immediate cancer treatment. OC is presented as their (or their daughter's) only viable option for preserving fertility, as their cancer treatment must begin immediately due to the severity of their (or their daughter's) cancer diagnosis. Survey participants were given varying levels of success for the OTC procedure: one-third of respondents were told that OC had a 25% success rate, another third were given a success rate of 50%, and the rest were told that OC is 100% successful. Within each survey, the given success rate of the procedure was consistent. Respondents were then asked to report their WTP for a variety of goods and services (such as a cell phone and a plasma screen TV), several medical interventions (including ACL surgery), and OC. Because some of these goods and services can be very costly, we told respondents that, if necessary, a payment plan could be created to allow them to borrow the money to pay for the good or service and pay back the cost over time.

We also used CV methods to inquire about the WTP for lifetime insurance coverage for the OC procedure. In theory, this valuation should depend on (a) the WTP for OC, (b) the expected cost of the OC procedure, and (c) the probability that OC will be required. Participants were told that OC would cost approximately $30,000. After several questions that required the respondent to think about probabilities and attitudes toward risk taking, we posited that 1% of women would be candidates for OC. Respondents were then asked whether they would be willing to pay for insurance to cover the cost of the OC procedure and, if so, how much they would be willing to pay annually for insurance to cover the cost of OC. Based on this information, risk neutral respondents should have a WTP for OC insurance of $300 if they valued OC at $30,000 or higher or 1% of their WTP if they valued OC at less than $30,000. Thus, the upper bound on the willingness to pay for insurance should be $300 plus a risk premium.[4]

The survey samples consisted of 75 young women from the Chicago area. We recruited all respondents through the posting of flyers at local undergraduate and graduate campuses throughout the city. By and large, the respondents consisted mostly of either students or employees of Northwestern University. The surveys were delivered in a one-on-one interview format with the same interviewer performing all interviews.

For the most part, respondents reported usable answers for nearly all questions. Some respondents, however, reported being willing to pay "whatever it took" for some of the medical procedures in the survey, including OC. In order to estimate means of these willingness to pay values, we set these respondents' WTP equal to the maximum finite WTP given by other respondents.

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[4] Individuals whose WTP for OC equals or exceeds $30,000 should be willing to pay at least $300 for insurance, which is the actuarially fair value. Those who value OC at less than $30,000 might prefer not to purchase insurance at $300 unless they are very risk averse.

## Results

Our analysis yielded meaningful results about the willingness to pay for the OC procedure itself and insurance to cover the cost of this medical operation. Table 27.1 reports summary statistics for the CV questions on the willingness to pay for the OC procedure among the sample of young women. The mean WTP for OC is a high monetary amount and, as evidence by our results, even a modest success rate of 25% is highly valued among this cohort. Note also that WTP does not display a "certainty premium," whereby the WTP for 100% success is disproportionately larger than WTP for smaller success probabilities. Instead, the WTP for OC is relatively consistent across varying success rates for the procedure. The nonlinearity in WTP as a function of the success rate may reflect the valuation of hope, as described by Becker et al. [5]. In other words, individuals highly value the possibility of being able to bear children, independently of the actual probability it will occur.

**Table 27.1** WTP for ovarian cryopreservation

| Good/service | WTP (mean) ($) | WTP (SD) ($) | Median ($) | Interquartile range ($) |
|---|---|---|---|---|
| OC – 25% success rate | 16,304 | 20,538 | 7,000 | 2,000–23,000 |
| OC – 50% success rate | 17,360 | 17,300 | 10,000 | 5,000–25,000 |
| OC – 100% success rate | 33,160 | 50,745 | 20,000 | 5,000–40,000 |

Our analysis also compared WTP for the OC procedure against WTP for a number of other common goods and services, in an attempt to assess the relative value of OC. Table 27.2 reports summary statistics for WTP for a big screen TV, a Toyota Corolla, and ACL surgery. The mean valuation for OC is significantly higher than the mean valuation for the television and the new car ($p < 0.05$, two-sided $t$-test). The mean WTP for OC, however, is not statistically distinguishable from the mean for ACL surgery ($p = 0.52$, two-sided $t$-test). Slightly more than half of the respondents (55%) were willing to pay more for OC than for a new car and the same percentage were willing to pay more for OC than for ACL surgery. Put another way, among our sample OC is more valuable than a new Toyota Corolla and about as valuable as ACL surgery.

As per the previous discussion, if respondents were risk neutral, their WTP for OC insurance would equal $300 if they valued OC at $30,000 or higher, or 1% of

**Table 27.2** WTP for OC and other goods and services

| | WTP (mean) ($) | WTP (SD) ($) | Median ($) | Interquartile range ($) |
|---|---|---|---|---|
| Big screen television | 729 | 837 | 500 | 250–1,000 |
| Toyota corolla | 15,891 | 10,716 | 15,000 | 10,000–30,000 |
| ACL surgery | 27,385 | 42,041 | 15,000 | 5,000–25,000 |
| OC – all success rates | 22,274 | 33,604 | 10,000 | 5,000–30,000 |

**Table 27.3** WTP for OC insurance

| Good/service | WTP (mean) ($) | WTP (SD) ($) | Median ($) | Interquartile range ($) |
|---|---|---|---|---|
| OC insurance – 25% success | 644 | 1,363 | 100 | 0–500 |
| OC insurance – 50% success | 573 | 932 | 320 | 0–800 |
| OC insurance – 100% success | 565 | 936 | 150 | 0–1,000 |

their WTP if they valued OC at less than $30,000. Table 27.3 describes the WTP for OC insurance across varying reported success rates of the procedure. Of the 65 respondents willing to pay a positive amount for OC, 22 out of 65 (34%) were not willing to pay any amount for OC insurance. Among these 22, the mean WTP for OC was $21,468 and 6 had a WTP for OC of $30,000 or higher, which exceeds the posited cost of treatment. Thus, a nontrivial fraction of respondents reports economically irrational valuations.

## Discussion

Our results demonstrate that the young women in our sample value fertility preservation more than they value a new Toyota Corolla and about the same as they value surgery to repair a torn ACL. Although respondents were at an age where they may have more limited responsibility for financial decisions (18–25), this sample was able to place reasonable values on all of the consumer goods listed (cell phone, television, new car, and car safety system). Our results indicate that the calculated values for WTP for OC are reasonable both relative to other goods and services and in absolute terms.

Unfortunately, the survey did not yield reasonable results for WTP for insurance to cover the cost of the OC procedure. The correlation coefficient for OC and OC insurance was about 0.08. However, this appears to have been a problem in the Neumann and Johannesson (1994) study as well, where respondents' WTP for insurance was well above the actuarially fair value implied by respondents' WTP for the procedure itself (implying a very high degree of risk aversion). We conclude that individuals may find it difficult to evaluate the set of probabilities required to determine a reasonable value for insurance.

## Conclusions

As fertility preservation technologies continue developing, the health-care marketplace needs to anticipate how these medical procedures will operate on an economic and actual level. Finances are a real concern for a large majority of Americans, and understanding the economic value that young women place of fertility preservation in the hypothetical situation of cancer can help clinical care providers and insurance companies alike to shape their policies, procedures, and recommendations.

The preliminary results of our survey are important for a number of reasons. Our results suggest that young women see OC as more valuable than a new Toyota Corolla and about as valuable as ACL surgery. The perceived value of OC among this sample is thus relatively high. Finally, our inconclusive results on WTP for insurance coverage point to need for continued research around this topic to better understand how the insurance marketplace can integrate OC into its existing structure.

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# Chapter 28
# Perspectives on Oncofertility from Demography and Economics

**Rosalind Berkowitz King**

## Introduction

The science of demography focuses on the drivers of population dynamics: fertility, mortality, and migration. Demography is inherently interdisciplinary and draws on theory from a range of social sciences, including sociology, economics, and anthropology. The demographers' approach to fertility research at a given time is grounded in the contemporaneous fertility trends and fertility-related technology at the societal and individual levels. For example, the founding of demography at the turn of the twentieth century coincided with declining fertility levels among the most affluent and educated families, a bimodal pattern of high fertility or childlessness among families at the lower end of the socioeconomic spectrum, and Margaret Sanger's public health efforts to support the availability of contraception. Thus, demography was originally deeply concerned with fertility control as defined by the ability to stop having children after reaching the desired family size. As US fertility patterns settled into nearly universal parenthood with most families having two to four children in the 1950s, demographers turned their attention to "uncontrolled" fertility in the developing countries of Asia and Africa. The most consuming fertility issues of the 1970s reflected the technological development of the contraceptive pill and the social development of increasingly non-legitimated teen births.

In the twenty-first century, much about fertility has changed. Some lines of differentiation in fertility patterns among Americans have lost their influence, as seen in the general convergence in completed family size across religious backgrounds. Many more methods of contraception are available and access to knowledge of these technologies has generated fertility declines for families across the world except for parts of Africa. But fertility-related technologies for creating and maintaining pregnancies have only become highly developed in recent decades, and their use has not yet become widespread enough to make an impact at the societal level (for a first analysis, see the work of Hoorens and colleagues [1]). Demographers today spend

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less scientific effort on fertility control as traditionally explored, but they have not yet felt a strong impetus to research aspects of fertility control such as the power to create children around barriers. The science of contraception is well documented and the science of infertility is scant.

Nevertheless, the sociological, economical, and anthropological concepts on which demographers have drawn to explain fertility patterns and contraceptive behavior can be usefully applied to infertility. Here, I begin to lay out how demographic theory and concepts from economics can shed light on questions of interest to researchers in the emerging field of oncofertility, the preservation of biological fertility in cancer patients.

## Why Have Children in the Twenty-First Century?

Before considering oncofertility specifically, we should consider more generally why individuals and families today desire to have children. Historically, people did not have a great deal of choice about having children. Sex and reproduction are basic biological functions, and the former, a popular activity, generally led to the latter [2]. The social construction of specific family forms and rules for who could join with whom to create a family provided some control over the frequency of sexual partnering but not over its outcome. Societies developed institutions such as craft guilds and nunneries and informal systems such as fostering to provide outlets for parents to dispose of children for whom they were either unable or unwilling to care.

When contraception becomes available and socially accepted, fertility declines and the decline is often steep. Current total fertility rates in the most developed societies range from a low of 1.2 in Poland to 2.0 in the United States. However, childlessness is still a minority status, reaching a recent high of 20% among women ages 40–44 in 2006 [3]. People apparently want children, just not very many of them.

Since mortality is inevitable, all social entities – individuals, families, communities, and societies – must reproduce in order to continue their existence into the future. The two main goals of individuals and society are production and reproduction: to make and consume material goods and to make members who will continue those processes and actions. But the time and resources needed for production and reproduction are finite, and thus individuals and societies need to make choices about how to allocate scarce capital. Economics is the social science that studies these decision-making processes.

The first economic theories of fertility came from classical and neo-classical economics. Classical economics viewed individuals as rational actors whose decisions were grounded in reason. Neoclassical models such as Becker's "New Home Economics" allowed for motives such as altruism but incorporated them logically into the utility maximization model [4]. A rapidly developing subfield within contemporary economics is behavioral economics, which blends insights into human behavior from psychology into economic models of decision-making. Behavioral economics allows that the decision maker may act from a position completely driven by emotion or non-rational motives. (Economists agree that rationality and emotions are both cognitive processes; whether or not they are exclusive of each other is a matter of debate.)

The most important aspect of economics for bioethicists is that economics is not concerned with morality. Classical economics aims to explain supply and demand for goods and services as determined by the behavior of rational actors with "perfect" information in free markets. Values are encompassed in the preferences of rational actors; preferences are stable and generally relegated to the error term in statistical equations. Neoclassical and behavioral economics allow for more complicated thought processes but still refrain from discussions of "right" and "wrong." Economists study topics such as discrimination and organ selling, but they argue only the circumstances and outcomes without making statements about whether such activities should or should not be pursued.

In the sections that follow, I list several concerns presented by interdisciplinary scholars at the annual humanities and social sciences meeting of the Oncofertility Consortium. Under each question, I provide an economic concept and suggest how it could be usefully applied to the existing discussion. These suggestions are admittedly sketchy in nature and I leave a more full development of each to future work by interdisciplinary researchers. I encourage oncofertility investigators to utilize the reference list presented here for a more comprehensive understanding.

## How Can Economic and Social Demography Help Us to Understand Oncofertility?

### *Why Would Patients Pursue Fertility Preservation Rather than Adoption?*

#### Risk, Information, and Uncertainty Reduction

On a purely theoretical basis, the rational actor has perfect information about the various courses of action available to her to pursue. In practice, information is always imperfect, and the accompanying uncertainty generates perceptions of risk for the actor. The transition to parenthood is particularly challenging because it most often requires making a permanent commitment to an individual whom one has never met and thus about whom one has little to no information. In the case of biogenetic childbearing, actors rely on their knowledge of themselves, their partner, and their own families of origin to predict the characteristics of the potential child. The motive of uncertainty reduction is one reason that biogenetic childbearing is preferred to the use of donor gametes, gestational carriers, and adoption. In each of those cases, the parents will have less information about and control over genetically transmitted traits, the intra-uterine environment, or both. While adoptive parents may have the opportunity to meet the child before committing to parenthood, this advantage of current knowledge is undercut by lack of knowledge about the child's life experiences to that point; Americans place a great emphasis on genetics and early rearing and view taking responsibility for a child for whom they have not controlled those factors as risky [5].

For oncofertility patients, a significant piece of information about their genetic heritage is the likelihood of a predisposition to cancer. In the case of a child with a genetic condition for which testing can provide information about the likelihood of the same disease appearing in genetically related siblings, a physician's duty to warn requires him or her to alert the parents [6]. But in the private context of biogenetic parenthood, the use of this kind of information with regard to decision-making about the child's reproductive future is left to the family.

In contrast, if the child wishes to adopt once he or she becomes an adult, that genetic risk is perceived as relevant information by adoption agencies. The guiding principle of the agencies is the best interest of the adoptee child, and pilot research from the Oncofertility Consortium suggests that agency staff perceive cancer survivors to have a greater risk of illness or death during the adoptee's childhood than the average prospective adoptive parent (see Gardino, Russell, and Woodruff in this edition). Researchers could apply demographic modeling techniques to cancer survivorship and morbidity data to assess the validity of the agencies' concerns about survivors' likelihood of becoming ill again or dying compared to the general population of adults with similar demographic characteristics. Thus, cancer patients pursue fertility preservation because they perceive that avenue to parenthood as more certain than alternatives such as adoption.

## *Why Do Some Patients Pursue Fertility Preservation When It Is Unlikely that They Will Produce Usable Gametes or Survive to Use Them?*

### Value

Cancer patients may value fertility preservation methods, such as ovarian tissue cryopreservation, even when there is a low probability of their survival or the success of the procedure. Economics identifies several types of values that may be useful to understand this patient perspective. Value may be thought of as the measure of what someone would give to obtain something or require in order to let go of something; value may also be conceptualized as the utility that an individual gains from something. We assign use value to goods and materials that we use, such as personal clothing and cars. We also assign existence value to goods and materials that we do not use. For example, many people are happy to have a portion of their taxes provide support for federally funded parks and recreation areas such as Yellowstone National Park that they will never visit. But they gain value of some kind from the fact that the park is there to be used in theory. Cancer patients may gain a kind of value from the potential that they perceive in the ovarian tissue.

### Normative Life Course

Cancer patients with uncertain survival may seek to reduce uncertainty in other areas of their lives. Fertility preservation may offer value in that arena as a way of maintaining the potential for biogenetic parenthood as a framework for the future after illness. Friedman, Hechter, and Kanazawa have noted the potential of childbearing as a strategy for uncertainty reduction [7]. Children are consumer durables so their presence provides a structural constraint of almost indefinite duration. The modern era of the late twentieth century was noted by Giddens [8] and other social theorists for its lack of societal cues to guide individuals in constructing their life narratives. In the 1950s, the constraints that sent mainstream Americans straight from high school or college into marriage and then a decades-long job for men or stay at home motherhood for women were stifling yet at the same time provided great security by answering huge questions about how to construct adulthood. The freedom that later generations experienced, and current generations are afforded, also creates anxiety. One way to master that anxiety is to generate limiting frameworks on oneself at the individual level, and having a child is a strong method for doing so. Following the decline in marital stability since the 1970s, the parent–child relationship is possibly the most strongly institutionalized interpersonal relationship, particularly for women.

### Reference-Dependent Preferences

Within behavioral economics, prospect theory proposes that individuals also assign unequal weights to probabilities, overweighting small probabilities and underweighting large probabilities [9]. In the case of oncofertility, the patient will therefore assign greater importance to the small probability of survival and less importance to the large probability that the fertility preservation procedure will not produce useful results (or conversely assign great importance to the small likelihood of being able to use the materials obtained through the procedure and less importance to the large likelihood of mortality). As seen in the pursuit of repeated *in vitro fertilization* (IVF) attempts by otherwise healthy individuals, patient behavior in this realm is generally to persist even in the face of great odds.

Prospect theory also suggests that we are more motivated to avoid loss than to achieve gain and that regret is a highly undesirable emotional state [9]. The least preferred outcome imaginable by the oncofertility patient is that she will fail to act to preserve her fertility and will then survive to a position in which she could have used the tissue or embryos obtained. A futile effort at fertility preservation still enables avoidance of a lost opportunity, an option that could have been available had one pursued a different course of action in the past.

## *Who Should Make the Decision about Fertility Preservation When the Patient Is a Minor?*

### Utility, Maximizing Behavior, and Altruism

Preferences shape individuals' utility functions. Utility is a measure of the relative satisfaction from, or desirability of, the consumption of various goods and services. Utilities across all goods and services are aggregated into a single functional form for each person, and then those curves may be further aggregated to represent the utility of families and societies. Individuals, families, and societies engage in maximizing behavior in order to derive the highest level of utility possible given circumstances such as the availability of goods and services and the resources that can be mobilized to attain them. Individuals who have positive preferences for children would thus incorporate children at a value of their own assignment into their utility function if doing so maximized utility. This incorporation occurs at the aggregated levels of family and society as well.

Not every individual and family will assign a positive value to future fertility. As noted above, from the perspective of Becker's new home economics, children are consumer durables, as they are not destroyed by use and are expected to have a long life span. Obtaining and investing in a child is a long-term commitment and involves extensive costs. (This perspective has been heavily critiqued [10] but it is a useful heuristic.) In the case of pediatric cancer patients, a conflict may arise between the preferences of the child and the parents. One possible solution to the dilemma lies in parental altruism. Becker states that parents incorporate the child's utility function into their own [11]. Consequently, parental utility is maximized when their child's utility is also maximized. Since parents are of an age at which the maturity to consent is generally assumed, then parents should inherently make the best decision for their child, as they are presumably acting in a way to maximize their own utility.

## Salience of Available Information

The age range of oncofertility patients spans from young children, of whom we can confidently say they are unable to give informed consent, to adolescents, whose cognitive and emotional development is in great flux, to young adults, who may still be financially and emotionally tied to their parents but who are legally formal decision makers. The diverse age range of these patients means that the level of information they can process and conceptualize about their true fertility preferences varies greatly.

Information is a central concept in economics, which classically focuses on the rational actor. Rational actors have a level of information about themselves, their situation, and their future. Based on this information, they make reasoned decisions. In the current case, information is highly problematic. First, information about how much one will enjoy parenting is always speculative until a child enters one's life. In the case of a minor, this information is even more tentative, given that the holder of the information is a child himself or herself, likely with little experience of caring for a dependent or having peers who are doing so. Decisions to parent are generally endogenous to marriage and education, and minors are unlikely to be married and likely still in the process of attaining their education. So future desires for a child are completely theoretical at age 4 (no information), highly theoretical at age 14 (possible experience babysitting and some idea of whether or not continuing education beyond high school), and somewhat theoretical at age 24 (normative "on-time" college graduation has or has not occurred, timing of entry into full-time work and first occupational status likely now observed, some romantic relationship experience, may have friends who have become parents).

Individuals also systematically expect their future preferences to be too close to their present preferences [12]. This tendency suggests that minors can be counted upon to misperceive their own wishes to have future children or to remain childless in comparison with grown women. This insight does not suggest that parents may be better at predicting for their child, but it is another strike against the child herself.

### Time Preferences and Time Perspective

Economists note that individuals have time preferences when they engage in consumption. Because the here and now is more concrete than the hypothetical future, individuals assign a greater value to goods and services that they can have now rather than those that they must wait to obtain later. Thus, given the same item, we discount its value if we cannot have it in the present. For example, an apple today is worth \$0.50; an apple tomorrow is worth \$0.25; and an apple next week is worth \$0.01, if an individual were asked to pay for it right now. This model is useful for thinking in general about how oncofertility patients may have a demand for fertility preservation, but we need a developmental perspective to apply this model to the question of whether the minor or the parent should make fertility preservation decisions.

Psychologists approach this aspect of decision-making through the concept of time perspective, which assesses the influence of an individual's consideration of past, present, and future in their decision-making processes [13]. Time perspective is correlated with health behaviors in adults but the effects are tied to educational levels [14], which are still in process for children. Planning and control processes show a developmental pattern from the stages of childhood into adolescence and young adulthood [15], so an investigation of these psychological aspects of decision-making for oncofertility patients may provide useful evidence for bioethicists.

## *Should the Public Support the Provision of Fertility Preservation Procedures and Services?*

### Externalities and Public Goods

Economic theory is also useful to frame questions about whether society has an interest in whether or not a given individual reproduces. Society has a vested interest in supporting public goods: goods that, once provided, can be consumed by additional others at no marginal cost and goods with both positive and negative externalities (which are consequences of activities that are experienced by third parties, not those directly involved in a transaction). The positive externalities, or benefits, of children to society extend from their ability as a future generation of workers to provide a basis for taxation on which to fund the growth of transfer payments through Social Security and Medicare [16]. The future generation of children also provides our society with social reproduction by fulfilling their role as the next generation of “Americans.”

Two imperfections exist in the creation of children at the societal level which have echoes at the individual level. First, certain children are worth more to society in terms of their future productivity and other children require remediational investment in order to reach this level [17]. Second, certain children are more pertinent to a society’s social reproduction than others [18]. These societal problems translate down to the individual level as reasons for developing technology such as fertility preservation for cancer survivors. Using genetic material from others, having another carry the child, or adopting a child are viewed as inferior options because the quality of the child and the ability of the child to serve as a replacement for the parent in the next generation are both called into doubt.

But establishing the production of children as a public good also invites state regulation into the arena of reproductive practices. We accept as a principle of our system of government that states have the right to pass laws to address issues that are legitimately of interest and concern to the public [19]. Externalities create market imperfections that states use legislation to fix. For example, parks and recreation areas are public goods that are not rational for a given individual to provide. Thus, states will use their powers of taxation to collect funds for them and then authorize government entities to construct and maintain them.

But while states are justified in using their powers to create programs such as Head Start to attempt to remediate the child quality problem at a societal level, the proposition that states have the justification to intercede at the individual level to influence which persons can reproduce biologically is highly contentious. Reproductive rights are constitutionally protected and states must have a compelling interest in order to override rights in that category. Economists have assessed the impacts of aggregated patterns of reproductive behavior on societal outcomes such as crime rates [20] and adult human capital [21], but they do not translate those findings back down to prescriptions for allocating access to reproductive technologies of any kind, from condoms to IVF.

## Conclusion

This chapter highlights selected concepts from economics that researchers in oncofertility may find useful. Demography draws on a range of social sciences including sociology and anthropology, and bringing theories from these fields is likely to prove fruitful as well. While oncofertility brings together two fields of medicine, its practice is fundamentally grounded in the very social process of family formation, and its meaning to individuals and society can only truly be understood within that context. These economic concepts can help to shape the evolving discussion around fertility preservation for cancer patients, offering new perspectives on these important questions and strengthening the overall discussions in this field.

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## Chapter 29

# For the Sake of Consistency and Fairness: Why Insurance Companies Should Cover Fertility Preservation Treatment for Iatrogenic Infertility

**Lisa Campo-Engelstein**

There is much debate not only about the morality of assisted reproductive technologies (ART) but also about how they should be classified. Should ART be understood as medical treatment for a disease (infertility) or should they be relegated to boutique medicine where they are seen as elective? How we answer this question affects our thoughts about whether ART should be covered by insurance companies. Those who claim infertility is a medical disease usually advocate that ART be covered by insurance. Conversely, those who believe ART are elective procedures generally oppose insurance coverage, insisting that insurance coverage should be limited to medically necessary treatments. While the debate cannot simply be reduced to whether "real" diseases should be covered by insurance and all other conditions should not, in the minds of many, a strong connection exists between what is considered a disease and what insurance should cover. For the purposes of this chapter, therefore, the belief that medically necessary conditions should be covered by insurance whereas elective conditions should not will serve as the basis of the discussion.

Most discussions of ART focus on their use in two circumstances: first, to treat people currently suffering from infertility due to disease (e.g., endometriosis) or unknown cause, and second, and more recently, to provide "insurance" against age-related infertility for women who plan to delay childbearing. Though still a contentious issue, the former – disease-induced infertility – is typically thought to be more deserving of insurance coverage than the latter – age-related infertility – because the cause of infertility is a disease, a "legitimate" medical problem rather than an individual's action. Indeed, some have argued that insurance should cover treatment for the underlying disease that is causing infertility (e.g., open a blocked fallopian tube) even if they do not think they should cover ART (Gerrity, 2009, Executive Director of the Oncofertility Consortium, Personal conversation). The perceived cause of age-related infertility is, in contrast, not often seen as legitimate

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but rather as the result of individual women's bad choices and selfishness. According to this view, women's desire to have a career leads them to delay childbearing, which is no one's fault but of their own (Goold and Savulescu discuss, and argue against, this position) [1]. In short, age-related infertility is not a medical problem and thus should not be covered by insurance.

Although my discussion in this chapter centers on infertility and insurance coverage, it diverges from these other debates in two significant ways. First, I will bypass the question of whether infertility should be classified as a disease. Second, I do not deal with disease-induced or age-related infertility; rather, I focus on another circumstance in which one might use ART: before undergoing necessary medical treatment that may lead to infertility. Specifically, I am concerned with fertility preservation procedures for cancer patients about to receive chemotherapy and/or radiation, both of which often cause infertility. I will refer to this type of infertility as iatrogenic infertility.

An iatrogenic condition is a negative side effect or adverse condition that is caused by the diagnosis, manner, activity, or treatment of a health-care provider. I recognize that this is a loaded term (which insurance companies and providers typically do not like to use), in part because some see it as a normative term implying providers' wrongdoing and blame. While this term encompasses negligent iatrogenic conditions, such as a surgeon leaving a scalpel inside the body of a patient, in this chapter I am using it to refer only to non-negligent conditions. Non-negligent iatrogenic conditions occur when medically necessary treatments have unavoidable and/or unpredictable negative side effects, such as cancer treatment causing infertility, hair loss, or nausea. Providers are not to blame in these situations, as they face a no-win situation: in order to treat and hopefully save their patients' lives, they must also harm them. Unfortunately, the nature of certain cancer treatments, as well as various treatments for other diseases, is inherently harmful (e.g., destroying healthy cells along with cancerous ones).

Insurance companies generally cover treatment for iatrogenic conditions that result from cancer treatment, even though they do not cover these same conditions when they are "naturally" occurring. Infertility treatment, on the other hand, is typically not covered, regardless of whether it is iatrogenic or naturally occurring. One reason many insurance companies refuse to cover ART is that they are often viewed as elective procedures, not medically necessary ones. However, based on insurance coverage patterns for other "elective" procedures performed in response to iatrogenic conditions, insurance companies should also cover ART, specifically fertility preservation treatment (i.e., cryopreservation of eggs, embryos, or ovarian tissue for later use), for female cancer patients. In this way, insurance companies will maintain consistency and promote fairness, since fertility preservation does not differ significantly from other treatments for iatrogenic conditions they already cover for women. While my focus is on female fertility preservation, one could presumably make a similar argument that male fertility preservation should be covered by insurance.

In order to support this claim, I compare ART for iatrogenic infertility to breast reconstruction surgery following lumpectomy or mastectomy, which is generally covered by insurance. I choose this comparison because just as in the case of infertility, there is probably not agreement on whether breast construction surgery for women who naturally have only one breast is medically necessary or elective. While I recognize that having only one breast is rarely, and perhaps never, a naturally occurring condition, this comparison makes for a good thought experiment. I will briefly explore the different ways of understanding and classifying this condition to highlight the discord.

Most would agree missing a breast is not a life-threatening situation. However, it would probably adversely affect a woman's quality of life. For example, surveys have shown that the loss of a breast makes women feel like less feminine – that is, less of a "real" woman – and I imagine women born without a breast would have similar emotions [2, p. 164]. Moreover, women without two breasts may also make others feel uncomfortable because these women do not have all the typical feminine gender markers (e.g., gender markers include breasts, hips, long(er) hair, and lack of facial hair). Indeed, the social response to women with one or no breasts may mimic the social response to people who are intersex, as their physical appearance does not match the "normal" female or male body. Yet, some have argued that the condition of intersex is largely a social, not medical, problem as it generally does not cause any physical health problems and instead causes strong cultural discomfort by blurring and confusing the gender lines (see Alice Dourmat Dreger, for example) [3]. Likewise, one could claim having only one breast does not lead to physical health problems, only personal and cultural angst, so it should not be understood as a disease in need of surgery. Those who support a narrow, scientific definition of disease based on biological functioning may agree that having only one breast does not require treatment and may assert that this condition is just an anomaly like six fingers. Constructionist perspectives on disease echo this belief, insisting that not all anomalies are diseases: "to call something a disease involves both a claim about the abnormal functioning of some bodily system and a judgment that the resulting abnormality is a bad one" [4, p. 3]. According to this view, classifying a condition as a disease is a normative claim, so determining whether having one breast is a medical condition involves drawing on one's own subjective values and judgments. Some may concur that having one breast engenders social problems, not physical health problems, yet still view this condition as a disease in need of treatment. This claim relies on a broad definition of health, like the one used by the World Health Organization: "health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [5]. Under such a definition, having only one breast would be considered a condition that interferes with one's social and mental health and quality of life. Consequently, it should receive treatment.

The above discussion shows that there is probably not much consensus on whether surgery for women who naturally have only one breast is medically necessary or elective. The same is true for ART to treat infertility: there is little agreement on whether these procedures are medically necessary or elective. This similarity is important because while breast surgery is covered by insurance when iatrogenic, probably not all insurance companies would cover this surgery when it is naturally occurring. As such, even though ART are often not covered due to differences in how infertility is understood and classified, insurance companies should cover ART in cases of iatrogenic infertility because it promotes consistency and fairness.

However, the case for insurance coverage for iatrogenic infertility using the above comparison may remain unconvincing due to the small prevalence of women with only one breast. A more common condition for which there would probably be greater consensus about its treatment as elective is asymmetrical breasts. While having only one breast is rarely, and perhaps never, a naturally occurring condition, naturally occurring breast asymmetry is quite common. Insurance companies rarely cover surgery for naturally occurring asymmetrical breasts and I imagine most people would agree with this decision. Breast asymmetry is rarely as conspicuous or socially isolating as having only one breast, so it makes sense that it would rank lower on the list of conditions that should be covered by insurance. Indeed, surgery to "remedy" breast asymmetry is often put on par with other "purely" cosmetic procedures, such as otoplasty for "protruding" ears and rhinoplasty for "overly large" or "overly wide" noses. In sum, while these procedures can improve individual self-esteem and thus quality of life, they are not generally seen as anything other than elective.

While surgery for naturally occurring breast asymmetry is usually considered elective and thus not generally covered by insurance companies, surgery to resolve breast asymmetry that results from a lumpectomy is usually covered, implying that the procedure is medically necessary. Moreover, in the case of iatrogenic breast asymmetry, this surgery is covered regardless of whether the patient had symmetrical breasts beforehand. Likewise, breast reconstruction surgery following mastectomy is typically covered, despite the debate over whether breast construction surgery should be covered for naturally occurring "missing" breasts. This discrepancy in breast surgery coverage between iatrogenic and naturally occurring conditions can be explained, at least in part, by looking at causality. According to one view, iatrogenic conditions are caused by the medical realm and therefore the medical realm – specifically the insurance companies – should take financial responsibility. In other words, because members of the medical profession caused the harm – something they are not supposed to do – the medical profession as a whole must take responsibility for mitigating the harm. The same principles apply when naturally occurring conditions are thought to be caused by bad luck or, at times, by the individual herself. Since the medical realm is not causally responsible for these naturally occurring conditions, one could argue that they should not be financially responsible for them. At play in this connection between causality and responsibility is the static understanding of the body that dominates medicine and science. Briefly, this is the idea that the body stays the same over time and disease is aberration that must be eradicated to restore the body to its "natural" and "normal" state. If any alterations occur in the process of healing the body, health-care providers should do their best to fix them so that the person's body is as close as possible to her original state when they are finished.

Certain acts and laws were passed in order to institutionalize the medical realm's responsibility for iatrogenic harms. For instance, the Women's Health and Cancer Rights Act, passed in 1998, mandates that if health insurance companies cover the costs of mastectomy for cancer patients, then they must also cover the costs of breast reconstruction for those patients [6]. Health-care providers and insurance companies sometimes assume responsibility for iatrogenic harms by the way they code for billing. For example, breast reconstruction surgery following a mastectomy is coded as cancer treatment rather than elective treatment. By allowing treatments for iatrogenic conditions to be subsumed into the larger category of disease treatment, insurance companies are tacitly accepting financial responsibility to cover these treatments. In addition to breast reconstruction surgery, there are other treatments that may not be covered by insurance when the disease is naturally occurring (in part because treatment is not seen as medically necessary), but are covered when iatrogenic; for example, wigs following cancer treatment are usually covered, whereas wigs for thinning hair or "cosmetic" reasons often are not.

The same pattern of insurance coverage seems to exist, though more covertly, in the fertility/infertility realm. Although 14 states now have laws mandating insurance companies to cover infertility treatment under certain circumstances [7], many insurance companies refuse to cover naturally occurring infertility or fertility preservation treatments. Reasons that insurance companies give for why ART should not be covered include the following: in/fertility treatments are experimental, they do not treat an underlying disease but rather produce a desired outcome (i.e., a child), and they are an elective procedure not a medical one [8]. However, there is growing evidence that insurance companies are covering iatrogenic infertility resulting from cancer treatment. Although no formal studies have been done, anecdotal data demonstrate that insurance companies will sometimes take financial responsibility for iatrogenic infertility. At the Oncofertility Consortium, female cancer patients have the option to choose a fertility preservation method – embryo, egg, or ovarian tissue cryopreservation – before beginning cancer treatment. These fertility preservation treatments have been billed under a primary diagnosis of cancer and a secondary diagnosis of procreative management. Although there have been many appeals and much negotiation, so far insurance companies have covered this treatment for all of the Consortium's patients (Gerrity, 2009, Executive Director of the Oncofertility Consortium, Personal conversation). Fertile Hope, a nonprofit organization that provides reproductive information and support to cancer patients and survivors, also notes that some cancer patients have convinced their insurance companies to cover fertility preservation by claiming that insurance companies cover side effects of all other medically necessary cancer treatment and that infertility should not be different [9].

The trend toward covering ART for cancer patients with iatrogenic infertility is a move in the right direction, as it creates consistency in coverage policy instead of treating in/fertility differently than other iatrogenic conditions. However, some may argue that insurance companies should not cover these treatments because they differ in significant ways from treatments for other iatrogenic conditions.

One objection to insurance coverage for iatrogenic infertility treatment may be that some ART, in particular egg and ovarian tissue cryopreservation, are considered experimental procedures, whereas breast reconstruction surgery is an established procedure. By practice, insurance companies rarely cover experimental procedures.

Although the American Society for Reproductive Medicine still defines egg cryopreservation as experimental [7], this technology, especially egg freezing using vitrification, is improving rapidly and some in the scientific community no longer view it as experimental [10]. Additionally, egg and ovarian tissue cryopreservation are the only available options for young and/or single women to be able to have a child with a future partner, not a sperm donor. Creating embryos, the only “mature” technology, run the risk that the biological father could oppose transfer. As a matter of social justice, fertility preservation options that do not require sperm need to be available to women in order to ensure they will be able to have a biological child and with the man they choose.

A second objection is that insurance companies tend to cover iatrogenic conditions that currently exist, like hair loss from chemotherapy, or that will almost certainly exist, like loss of an entire breast following mastectomy, not conditions that may or may not exist in the future, like infertility. Yet, a low probability of occurrence should not lead providers to forgo prophylactic procedures to avoid iatrogenic conditions. In fact, providers typically provide treatments to prevent iatrogenic conditions that may or may not occur, such as antiemetics for nausea and dental evaluations for osteoradionecrosis. Health-care providers also often recommend storing one’s own blood as a prophylactic precaution in the case of an emergency transfusion. Whether the stored blood will be used cannot be predicted, but patients often want to be prepared for the worse case scenario. Those who seek fertility preservation treatment are similarly motivated as those who store blood: in a worse case scenario – where patients find themselves infertile after cancer treatment – these patients have a reserve of gametes to use to have biological children.

While treatment for most iatrogenic conditions generally occurs very soon or immediately after cancer treatment, in the case of fertility preservation, frozen embryos, eggs, ovarian tissue may not be used for many years, even decades. However, according to the principle of moral neutrality, the timing of a harm has no moral significance [11]. Consequently, the time at which a woman experiences the harm of iatrogenic infertility – whether it is 6 months or 6 years following treatment – does not change the degree of harm.

A third objection is that when insurance companies cover iatrogenic conditions that would not be covered when naturally occurring (e.g., breast surgery and wigs), part of the reason for doing so is that the results of the treatment, which are visible to both the patient and others, normalizes the patient’s gendered body and identity. Women without certain gender markers, like breasts or head hair, often feel less feminine, which affects their sense of self and quality of life. Moreover, others in society may feel uncomfortable with and act differently toward a woman whose physical appearance does not match the “normal” female body. Yet, fertility preservation treatment also normalizes women’s gendered body and identity in a visible way. In addition to the fact that motherhood is an important part of many women’s identity, there is a social expectation that women have children. Pregnancy is one of the most visible symbols of femininity, as is a woman caring for children.

A fourth objection to insurance coverage is that fertility preservation treatment is inherently more socially and ethically complex because it not only affects the individual patient but also involves and impacts her current or future partner, her family (e.g., her parents, children), and future offspring in ways that treatment for other iatrogenic conditions does not. While fertility preservation treatment is indeed more socially and ethically complex than other treatments, this difference is not pertinent to discussions of insurance coverage. Insurance companies often cover socially and ethically complex procedures outside of ART, including "corrective" surgery for intersex infants, fetal surgery, and genetic testing for hereditary diseases. The social and ethical complexity of the treatment should not factor into coverage decisions, though it may be an indicator that patients need extra counseling before making treatment decisions.

Unlike the first four objections, the last objection does not compare ART with other treatments that are covered. Rather, it deals with the appropriateness of providing ART to cancer patients because cancer patients do not meet the definition of infertility. When insurance companies do cover infertility treatment, it generally only applies to those diagnosed as infertile, commonly defined as the inability to conceive after 1 year of regular and unprotected heterosexual intercourse. Although cancer patients are not infertile at the time when fertility preservation treatment would take place (right before the commencement of cancer treatment), for many, infertility is an unfortunate inevitability following some treatments. While it is difficult to precisely predict a patient's chance of infertility, some treatments generally yield infertility rates of 80% or more [12]. Although it is true that cancer patients do not fit the standard definition of infertility, this does not mean that their need for infertility treatment is any less – in some ways, their need for infertility treatment is greater. Unlike traditional infertility patients who can continue receiving infertility treatment until they conceive, cancer patients often only have one opportunity at preserving their fertility as it must occur before they begin cancer treatment. The unique situation cancer patients face reveals the traditional definition of infertility as too limited, for it cannot account for the fertility preservation needs of those with foreseeable iatrogenic infertility.

As the field of oncofertility continues to develop and fertility preservation options continue to expand, insurance companies will increasingly be confronted with how to handle iatrogenic infertility for cancer patients. I have argued that ART for cancer patients are similar to treatments for other iatrogenic conditions that are currently covered by insurance and thus their exclusion from insurance coverage is unjustified. Insurance companies should, for the sake of consistency and fairness, cover fertility preservation treatment for cancer patients. Given the controversy surrounding reproductive technologies, this suggestion may be met with fierce opposition. However, it is time for insurance companies to stop relegating ART to a separate realm outside of "real" health care, especially when they cover treatment for conditions that could also be perceived as elective. The fact that insurance companies have begun covering fertility preservation treatment for cancer patients gives hope that fertility and infertility treatments are finally being taken seriously by insurance companies. Nevertheless, this coverage is done covertly on a case by case basis rather than under a blanket policy, which insinuates that insurance companies are still not ready to publicly assume financial responsibility for iatrogenic infertility (Gerrity, 2009, Executive Director of the Oncofertility Consortium, Personal conversation).

Perhaps a state or federal mandate, modeled after the Women's Health and Cancer Rights Act, is necessary for insurance companies to begin openly and universally covering treatment for iatrogenic infertility. Such a mandate would not only symbolize the importance of fertility preservation treatment and the severity of infertility as a disease but also open the door for more discussions between patients and providers about fertility preservation treatment. Furthermore, a mandate would provide greater access to patients from lower socioeconomic statuses, to patients without insurance, and/or to patients who do not have patient advocates to help them secure funding for this technology.

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# Part VI

# Repercussions of Oncofertility for Patients and Their Families

# Chapter 30
# Healthcare Provider Perspectives on Fertility Preservation for Cancer Patients

**Caprice A. Knapp and Gwendolyn P. Quinn**

## Introduction

For many people, cancer is the most feared health diagnosis imaginable and brings about immediate thoughts of death. Even cancer healthcare providers have been shown to exhibit a sense of hopelessness and negative attitudes toward a cancer diagnosis. Yet, overall cancer survival rates have been increasing over the past 30 years, suggesting that a diagnosis of cancer should not necessarily be associated with impending death or giving up hope of survival. Five-year cancer survival rates over the past 30 years have increased from 56 to 64% for adults and 56–75% for pediatric and adolescent cancers. As a result, there are approximately 450,000 cancer survivors in the current population between the ages of 19 and 39, and it has been estimated that by 2010, 1 in every 250 young people in the United States will be cancer survivors. Increased survival rates have caused a shift in thinking toward a more comprehensive model of cancer care. Survival and cancer treatment still take precedence, but recent focus among healthcare providers, researchers, organizations, and policy makers shows increased attention to the long-term psychosocial aspects of cancer survival. The National Institute of Medicine's 2001 compendium, *Crossing the Quality Chasm*, demands the healthcare system no longer focus on survival alone, but instead focus on "quality survival." Interest in the quality of life experienced by cancer survivors and a focusing on improving self-reported rates of quality of life have been on the forefront of the National Cancer Institute's National Cancer Plan, as well as part of the philosophy and policy of many organizations such as the Lance Armstrong Foundation and the Susan G. Komen Foundation.

In addition to ongoing physical and physiological effects from cancer treatment, cancer survivors often face financial, employment, social, emotional, and educational challenges. The physiological effects of chemotherapeutical agents and

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irradiation have been associated with a range of long-term impairments such as cardiac and lung dysfunction, hearing loss, alopecia, and neurological disorders. These same treatments have also shown to decrease fertility, or in many cases, cause permanent sterility. For the breast cancer patient in her fifties or the prostate cancer patient in his seventies, this loss may not be highly significant. However, to young men and women who survived cancer as a teen and dreamed of being a parent one day, this loss of fertility is often a devastating blow.

The exact risk of sterility from chemotherapy or radiation is not known and depends mostly on the age of the patient, the type of therapy, the site of the cancer, and the stage of the disease. Studies suggest that between 40 and 80% of female cancer patients are at risk of becoming infertile and between one-third and three-quarters of male cancer patients may become sterile following treatment for cancer.

Given the possibility that cancer patients might be faced with impaired fertility or sterility in the future, what options do they have for future childbirth and or parenting? The American Society for Clinical Oncology (ASCO) [13] and the American Society for Reproductive Medicine (ASRM) [12] recommend that physicians should discuss the risks of infertility with all cancer patients of reproductive age. They further suggest that interested patients should be provided with information to answer their questions about possible fertility preservation and should be referred to reproductive specialists and psychosocial providers as needed.

Interested male cancer patients have more straightforward options if they have already reached puberty. Males can bank sperm at a sperm banking facility or even in the privacy of their own home or hospital bed with mail-in kits. Pre-pubertal males may also have the option of experimental procedures such as cryopreservation of testicular tissue. Fertility preservation for females is more involved. To date, cryopreservation of embryos and ovarian transposition are the only non-experimental options available to women. Other experimental options include oocyte cryopreservation and ovarian tissue cryopreservation. One fact that impacts both males and females with cancer is that there is a narrow window of opportunity for pursuing fertility preservation. The most successful results are achieved among patients who preserve DNA prior to cancer treatment. These options are discussed in more detail in Part I.

Although addressing potential fertility loss may be overwhelming for newly diagnosed patients and their families, multiple studies suggest that failure to confront the possibility can cause regret and distress to cancer survivors and significantly impact their quality of life. Multiple studies with survivors, particularly adult survivors of pediatric or young adult cancer, suggest patients do not recall having a discussion about loss of fertility. It is not known if these discussions did in fact occur for the majority of patients but resulted in patients not remembering them or if the conversations did not take place at all. What is known is that the ability to parent a biological child is of great importance to cancer survivors. Several studies suggest that as many as 75% of childless patients who are diagnosed with cancer wish to have a child in the future. Studies conducted among survivors of pediatric cancer indicate a strong fear that they will be rejected by future partners due to their inability to have a child.

Current guidelines attribute the onus of these multifaceted conversations to oncologists. However, patient–provider interactions are complex and providing an optimal exchange of information along the continuum of care for cancer patients is challenging. The current ASCO guidelines perhaps fail to account for the fact that discussions about fertility preservation need to be ongoing and must be modified to meet the specific needs of each patient. For example, at the point of diagnosis, information on fertility preservation may not take precedence over information about survival. Healthcare providers should insist that patients and families hear and consider fertility preservation information regardless of patients being overwhelmed or distraught. During treatment, patients should be given information on how that particular treatment regime may affect their future fertility. Finally, after patients are cancer-free or have completed treatment, they may have questions about childbearing in regard to their health and the health of their potential offspring. Thus, discussing fertility preservation should not be viewed as a one-time task to be checked off on a care plan, but as an evolution of health information exchanges between healthcare providers, patients, and their families. Providing this information in a comprehensive, honest, and consistent manner may improve the patient's long-term health related to their quality of life.

## *Oncologists*

Given the important role that healthcare providers play in the dyadic exchange of fertility preservation information, it is critical to understand their perspectives, perceived barriers, and potential solutions in discussing fertility preservation with cancer patients. This section summarizes the existing fertility preservation evidence from healthcare providers who treat adult patients.

Physicians face many communication challenges when discussing fertility preservation with patients. These challenges can be related to (1) physician characteristics, (2) patient factors, and/or (3) healthcare system factors. Multiple studies with oncologists indicate that knowledge barriers can inhibit a discussion about fertility preservation with a newly diagnosed cancer patient of childbearing age. Two key knowledge barriers often faced by oncologists are: knowledge of where to refer patients and knowledge of fertility preservation treatment options. Although online directories do exist for sperm banking, physicians often cite that it is difficult to know where to refer a male patient. This is further compounded by lack of knowledge on the most up-to-date fertility preservation technologies, especially for females. As previously noted, several of these technologies are still experimental; however, without a basic understanding of available options, a physician may miss an opportunity to refer a patient with the mistaken belief that there are no options for the patient. In a study by Schover et al. [1, 2], a knowledge quiz was distributed to 162 oncologists who treat male cancer patients. The results showed that on average, most physicians answered only 10 out of 15 questions correctly. More than one-half of the physicians in the sample did not know that males were more likely to become infertile than females, overestimated the number of sperm samples needed, and did not know what the costs of sperm banking were. While about 90% of oncologists in this study indicated that sperm banking should be offered to men, only 10% noted they did so in routine practice. A 2009 study by Quinn et al. [14] conducted among a representative sample of US oncologists showed 25% did not know where or how to refer a patient for fertility preservations options.

There is less information available in the existing literature on patient factors that may serve as communication barriers. Several studies have identified communication barriers among those patients with low health literacy levels or those from cultures or religions that do not support assisted reproduction, as well as for patients who do not speak English. A qualitative study by Quinn with physicians at a single institution noted that the discussion of fertility was “Awkward enough but compounded in difficulty if done through an interpreter.”

Perhaps the most intricate patient issue that serves as a barrier for discussion is the patient who has late stage disease or a poor prognosis. Several studies of physician behavior indicated this key barrier to the discussion. Posthumous parenting or posthumous reproduction is a term used to describe a patient who stores sperm or embryos or other DNA and then allows the use of the stored materials for assisted reproduction with a partner or spouse after his or her death. In addition to some physicians’ attitudes that this is not an acceptable practice, others are unaware of this option for some couples or partnerships and thus do not suggest fertility preservations. As noted by one physician in a study on barriers to discussion of fertility with oncology patients, “I am very uncomfortable telling a patient that she has a 20% chance of survival and then adding, by the way, have you ever thought about having children?”

Another patient centered issue that serves as a barrier to discussion of fertility preservation centers on treatment delay. While males can typically pursue sperm cryopreservation within a day or two of diagnosis if an appropriate facility is available, females who are interested in cryopreservation often require a 2–6-week period of time for ovarian stimulation. In some cases where tumor resection is the first course of treatment for the patient, ovarian stimulation can occur during the healing period after surgery and before adjuvant or neo-adjuvant therapy begins. However, in other medical scenarios, most oncologists reported they would not recommend a female patient delaying chemotherapy to pursue fertility preservation. The oncologists’ recommendation that a patient should not delay treatment to use fertility preservation was often cited as a barrier to discussing fertility preservation options. A physician in the Quinn 2007 qualitative study noted, “It seems unfair to tell a patient there are options available to have a child in the future, but not for you, your cancer is too aggressive and if you want a better chance at survival you have to start treatment ASAP. I’d just rather not bring it up, especially if the patient has not brought it up.” Concerns about treatment delay are often intermingled with the concept of posthumous reproduction. While little research has been conducted on this concept from the patient perspective, some female patients have suggested that having a biological child in the future is as equally important to them as surviving. A female patient posted the following on a website for young cancer survivors, “My husband and I have discussed this at length, I'd rather have the chance to be pregnant and bring a child into the world than live without that experience. I've wanted to be a mother my whole life; it's all I've ever wanted. My husband knows he may raise our child alone. This is our choice. I appreciate the medical advice and the cautions but this is what we want."

Finally, there are healthcare system barriers for physicians attempting to communicate about sterility and fertility preservation with newly diagnosed patients. Physicians may have a high patient caseload and competing demands on the time that they have available to spend with each new patient. Quinn et al.'s [3] qualitative study of 16 physicians noted that time was scarce during office visits and therefore, fertility preservation was not necessarily a top priority for discussion. As one physician said, "You always do your best to cover all the bases but with an acute disease there is too much going on to think about."

Despite the existence of national guidelines by ASCO and ASRM, individual hospital-level policies or practice guidelines about fertility and preservation may not exist and as such, physicians may be either unaware of the need or be required to deal with each patient on a case-by-case basis. Educational materials do exist and are available from the Fertile Hope organization, the Lance Armstrong Foundation, and the Oncofertility Consortium. However, knowledge and distribution of these materials to patients by physicians is quite low. Quinn et al.'s [4] study of US oncologists showed less than 25% were aware of or distributed educational materials to their patients.

In addition to communicating the potential loss of fertility to patients and stating that fertility preservation options may be available, oncologists are also responsible for referring interested patients to reproductive endocrinology specialists. To date, Quinn et al. [4] has conducted the only national study of physicians who treat oncology patients in an attempt to understand their practice patterns and factors associated with referral to a specialist for fertility preservation. In total, 613 physicians across the United States were surveyed (response rate of 33%) and the unadjusted results suggest that less than one-half of physicians "always" or "often" refer oncology patients to a reproductive specialist when they have questions about fertility preservation. After controlling for several individual- and practice-level characteristics, the study also found that female physicians, physicians with a positive attitude toward fertility preservation, and physicians whose patients inquired about the effects of cancer treatment on fertility preservation were more likely to be referred to specialists as compared to their referent groups.

Overall, there have been few studies about adult oncology providers' views, practice patterns, perceptions, and barriers to discussing fertility preservation. Yet, the results are fairly consistent. Healthcare providers lack knowledge to address fertility preservation, and even though ASCO and ASRM have recommended that all oncology patients who ask for information receive it, and if appropriate, also receive a referral to a reproductive specialist, less than 50% of providers offer follow those recommendations. Healthcare providers have also indicated that fertility preservation materials should be improved and be created at appropriate language, culture, and literacy levels.

Although the existing literature for healthcare provider practice behavior is insightful, and a first step in improving fertility preservation outcomes for adult oncology patients, there are several gaps in the research that should be addressed. First, most of the existing evidence on providers is focused on oncologists and not on specific cancer specialists. In some cancers, such as breast cancer, a patient may meet with and be treated by a surgeon. This surgeon may serve also as the medical oncologist or may transfer the patient to the care of a medical oncologist after the surgery. In these cases, discussion of fertility preservation may fall through the cracks, with the surgeon assuming that the responsibility for the discussion of sterility falls in the domain of the oncologist prescribing the chemotherapy or the radiologist administering radiation. In every healthcare system, there may or may not be a policy or guidelines to address responsibility for the discussion. Furthermore, although almost every institution requires patients to sign a form understanding the risks and potential associated side effects of chemotherapy, one of which may be sterility, the signing of such a form does not constitute a discussion. It is not known if healthcare organizations have formal policies about fertility preservation and a process for referrals or care plans. Best practices in this field should be documented and shared by international, national, statewide, and local organizations. These are just a few examples of the type of information that is missing from the literature on healthcare provider's experiences with fertility preservation. This information could potentially be used to inform researchers, clinicians, healthcare organizations, and policy makers to better understand where resources can be allocated to most effectively and efficiently improve outcomes.

## Adolescent and Pediatric Providers

Perhaps even more daunting is the task that healthcare providers face when addressing fertility preservation with adolescent or pediatric oncology patients. Physician challenges range from being uncomfortable with having discussions with adolescents about sexuality and reproduction to discussing options with parents who are legally required to provide the consent for treatment decisions for adolescents. Compared to studies of healthcare providers who primarily treat adults, more fertility-related studies have been conducted with pediatric oncologists and pediatric oncology nurses who treat oncology patients. However, this may not be surprising given that survival rates are higher for pediatric and adolescent cancer and it follows that more of these patients will have to consider their future fertility as compared with adult oncology patients.

### *Physician Studies*

One of the first studies about adolescent fertility preservation was conducted by Achille et al. [5] and primarily focused on barriers and enabling factors for young men to bank sperm. In-depth interviews conducted with 18 healthcare professionals highlighted that healthcare providers consider the age of the patient when deciding to present information on fertility preservation. Results suggest that a supportive parent or partner was an enabling factor to bank sperm and patients typically did not view sperm banking as a complex procedure, although there were logistical problems in finding an available facility. Other barriers cited by the healthcare workers were cost, cultural beliefs, and sexual orientation. To date, no studies have been conducted that focus solely on female adolescent oncology patients.

A second study by Goodwin et al. [6] surveyed 30 healthcare providers in a hematology/oncology department (response rate 94%) about their attitudes and practices regarding fertility preservation. Although providers had high levels of knowledge about fertility preservation, about one-half were unaware that the risk of infertility is higher for males than females and that pregnancy outcomes of pediatric cancer survivors did not result in higher rates of birth defects. About 35% of healthcare providers routinely consult with a reproductive specialist and about 64% noted that it was difficult to find specialists and facilities for fertility preservation. Specific to adolescents, 86% of healthcare providers indicated that parents often ask about future infertility and the same percentage felt that adolescents should be included in fertility preservation discussions.

In a 2008, qualitative study of 24 pediatric oncologists in the state of Florida, Vadaparampil et al. [7, 8] identified physician, parent, and institutional factors that potentially interfered with fertility preservation discussion with adolescent and pediatric patients. Consistent with findings from the adult literature, about one-half of pediatric oncologists felt that they would like to learn more about fertility preservation, especially the options for females. Although none of the physicians in the study had received any training on the subject of fertility preservation, most were comfortable with discussing fertility with patients and families. Those who were not comfortable wanted educational materials that were more age-appropriate than the current available materials. All of the physicians indicated that they would not recommend delaying treatment for females and a few were unsure if they would recommend delaying treatment for males to sperm bank. Physicians cited that parents' emotional state and culture could be barriers to discussing fertility preservation. For example, many parents are overwrought upon learning their child has cancer and even when the child has a good prognosis they are unable to focus on issues of survivorship. As several oncologists from this study noted, "In cultures where assisted reproductive technology is not acceptable it can be difficult to discuss issues like sperm banking. This means talking about masturbation which can be uncomfortable for the parents and having this conversation through a translator can make it worse." Institutional barriers experienced by providers who care for adults such as cost, availability of educational materials, and lack of institutional guidelines were also cited as barriers for adolescents.

## *Nurse Studies*

Another unique factor about the available adolescent fertility preservation literature is the emphasis on nurses' perspectives. This is particularly important as some have argued that nurses have more direct interaction with oncology patients and their families, and perhaps might be better positioned to discuss fertility preservation. Under that framework, several studies have solely assessed pediatric oncology nurses' knowledge, attitudes, and barriers to fertility preservation.

Reebels et al. [9] surveyed 27 nurses about male adolescent fertility preservation (response rate 45%). As with physicians, nurses incorrectly indicated that females were at higher risk for infertility, they were not aware of costs of sperm banking, and only one-fifth knew that young men might have low sperm count and motility at diagnosis. Nurses noted that they would be less likely to discuss fertility preservation if the young man was HIV positive, had aggressive cancer, or was openly homosexual.

In 2007, Vadaparampil et al. [10] published two studies on pediatric oncology nurses' attitudes, practice patterns, and institutional barriers toward fertility preservation using data from a survey completed by 126 pediatric oncology nurses (response rate 65%). In the first study, the findings corroborate the low levels of physician adherence to the 2006 ASCO guidelines in that 73% of pediatric oncology nurses report discussing fertility preservation less than 10% of the time. In the second study, which focused on institutional barriers, the results showed that only 14% of the nurses indicated that their institution had fertility preservation guidelines on the offering of sperm banking, 8% had guidelines of the offering of ova cryopreservation for females, and three-quarters of the sample indicated that there was a strong need for these guidelines at the institutional level.

Finally, a study by Clayton et al. [11] compared pediatric oncology nurses' attitudes and knowledge about fertility preservation from 2005 to 2006. The importance of this study is that the ASCO guidelines on fertility preservation were released to the public in 2006, making this one of the few studies that can comment on changes in behaviors following the guidelines. Results from the surveys, however, showed little change between pediatric oncology nurses' attitudes about fertility preservation from 2005 to 2006 and 96% indicated that they were unaware of the ASCO guidelines. These results emphasize that creation of guidelines is only part of the answer to establishing best practices toward fertility preservation and that dissemination is equally, if not more, important.

The cost of assisted reproductive technology may be another barrier to discussing fertility preservation with oncology patients, particularly pediatric and adolescent patients. Although cost was rarely cited in physician studies as a primary barrier, other healthcare personnel such as nurses and social workers noted concerns in this area. Two studies examining knowledge and attitudes of nurses [10] and social workers [15] showed the costs associated with fertility preservation were a factor in dampening enthusiasm for discussing or referring a patient. The costs for sperm banking range from $250 to $500 for preserving and from $100 to $500 per year for storing the sample. Although nurses and social workers found these costs to be associated with their reluctance to discuss, the majority of young men who chose not to sperm bank cited not wanting children in the future or not having received timely information as their number one reason.

The costs associated with female fertility preservation are higher and more medically complicated. The average cost for embryo cryopreservation ranges from $5,000 to $12,000 and the costs of in vitro fertilization of stored embryos may also range from $10,000 to $25,000 a cycle and may require more than one cycle for a successful pregnancy. Nurses and social workers cited these costs as a barrier to discussing fertility preservation with females. One social worker reported, “We have patients who have no transportation for their treatment and who are living on public assistance. It doesn’t seem right to discuss this very expensive option with them when they can’t even afford their electricity bill.” While physicians are less likely to cite costs as a barrier, it is certainly on their mind. A physician who practices in a very low socio-economic neighborhood commented, “I’ve had to find shoes for my patients to go home in when they came to clinic barefoot. I’m not comfortable discussing let alone referring them to a specialist for a procedure that I know they can not afford.” The concern over referring patients to a reproductive endocrinologist or other infertility specialist was also cited as a deterrent among nurses and social workers. “It’s one thing to talk about a service the hospital can provide even if the patient can’t afford it, but it’s another thing to send them to a specialist knowing they can’t even afford the office visit never mind the procedure.”

In this collection of adolescent studies, several themes emerge. First, it is clear that decision making and ethics are a challenge to provider–adolescent communication and referrals to reproductive specialists. Physicians and nurses are faced with acknowledging the adolescent’s desires while legally looking to the parent for the ultimate decision on fertility preservation. Some states do have exemptions which allow minors to make medical decisions, but these are mainly focused on pregnant minors and minors who already have children. The law is silent on a minor’s rights to make decisions about their future children. Second, even when adolescents are included in the decision-making process it is not clear how healthcare providers should explain fertility preservation to them. Along the developmental trajectory, adolescents’ understanding of fertility preservation should evolve. Younger adolescents may understand that, “they may not be able to have a baby,” whereby older adolescents may understand that, “reproductive technologies could help them have a baby in the future if they are infertile.” Understanding appropriate terminology and messages is critical for developing fertility preservation educational materials specifically for adolescents and their parents. Studies that create and evaluate the effectiveness of these materials are needed. Third, adding to this complexity is the fact that understanding fertility preservation technology could be related not only to development, but also to parental provision of information on sexuality and reproduction. Fourth, although it is known that parents are the legal decision makers, there have been no dyadic, or even triadic, studies to understand where the views on fertility preservation may diverge or converge for adolescents, parents, and physicians. Finally, costs of procedures have been shown to be a factor in the discussion of fertility preservation with both parents and physicians citing this as an influence.

## Conclusion

Regardless if the oncology patient is an adolescent or adult, the need for additional provider education about fertility preservation is cited in the conclusion of almost every existing study. However, stating that education is necessary is marginally useful to medical educators and administrators when time, funding, and expertise are scarce. There is a critical need for studies to determine the most effective educational method to deliver fertility preservation education so that knowledge is increased and sustained in an effective manner. Studies on the educational methods of continuing medical education credits and residency education have shown that didactic training, while the most common method used, is the least effective. Randomized, multi-center studies should be conducted to compare educational methods such as standardized patients, teachable moments, seminars, and computerized training modules, noting that the "optional" model may differ by specialty type or level of overall experience. Without this important information, researchers and advocates will continue to point to lack of provider education as a primary barrier to fertility preservation without being able to make concrete suggestions on how to overcome that barrier.

Studies need to be conducted that begin to understand why certain patients were and were not referred to reproductive specialists. Although surveys are able to capture attitudes toward hypothetical referrals, in reality referrals from oncologists to reproductive specialists may differ by their willingness and ability. Retrospective chart reviews and follow-up interviews with oncologists might help to understand additional patient, family, and systematic barriers to referral. Perhaps these studies would illuminate the need for facility-based policies such as standardized forms or chart notes.

Longitudinal patient studies are needed to ascertain if, and how, fertility preservation information is being provided not just at the time of diagnosis, but during treatment, and later when survivors want to have children. Having a single brochure, pamphlet, or video may not be useful to providers, as different stages across the illness trajectory might require information to be delivered in a variety of ways. For example, do cancer survivors seek information on family planning from their primary care physicians, oncologists, or staff at a late effects clinic? Materials provided may need to be tailored to these specific practice settings.

There is limited evidence in the literature about the knowledge, attitudes, and perceptions about fertility preservation from other healthcare workers such as social workers, care coordinators, or case managers. In a managed care environment, the perceptions of these healthcare workers may be important, as they have increased interactions with oncology patients. Likewise, appropriate educational methods may differ for these professions.

Finally, more information is needed on how institutional practices, insurance coverage state laws, and other healthcare policies affect healthcare provider interactions about fertility preservation with oncology patients.

Research in the field of fertility preservation for oncology patients has been quickly changing. Social science studies, including the perceptions and impact of healthcare providers, are more important than ever. Although physicians and nurses are often in the first line of defense to counteracting decreased future quality of life for cancer patients, they must have the best tools available for that battle. Instead of focusing on what providers are not doing in regard to fertility preservation, research in this area must continue to evolve and begin to focus on how these improvements can be made. Ultimately, the goal is to improve the lives of cancer survivors; researchers and clinicians should work together to reach accomplish this mission goal.

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# Chapter 31
# Counseling and Consenting Women with Cancer on Their Oncofertility Options: A Clinical Perspective

**Emily S. Jungheim, Kenneth R. Carson, and Douglas Brown**

## Introduction

### *The Challenges of Counseling Oncofertility Patients*

Over the past decade, professional and lay organizations have raised awareness of the damaging effects some cancer treatments can have on the fertility of young women. Despite this progress, counseling and consenting cancer patients about their fertility remains complicated. Literature from the American Society for Clinical Oncology [1] (ASCO) outlines treatment regimens that may affect fertility; however, these regimens continue to evolve, making it difficult to predict how an individual's fertility may be compromised. After fertility counseling, some women elect to preserve gametes or embryos prior to cancer treatment, but doing so does not guarantee future fertility. There are risks involved with the procedures involved in acquiring these reproductive tissues. Furthermore, patients who elect gamete or embryo banking need to be counseled about additional challenges they may face – challenges predicted by the unique history of reproductive medicine.

This chapter details considerations and references we have found helpful in counseling and consenting cancer patients regarding their oncofertility options.

### *The Oncofertility Patient–Clinician Dialogue*

#### Risks of Cancer Care to a Woman's Future Fertility

Ideally, a cancer patient's physician initiates discussion about fertility preservation options soon after she receives her diagnosis and certainly before she begins treatment. Unfortunately, initiating the discussion is often the most difficult step in the oncofertility dialogue. Oncologists may be aware of the threat chemotherapy poses

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to fertility in general terms, but unprepared to address this threat in specific cases. To help guide oncologists and other clinicians in these discussions, ASCO released recommendations on fertility preservation for cancer patients [1]. This document was created in 2006 by a multidisciplinary group of professionals including oncologists and reproductive medicine specialists. The authors of these recommendations emphasize that "oncologists should address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to reproductive specialists" (p. 2917). They acknowledge, however, that data regarding infertility risks associated with common chemotherapeutic regimens in women "are poor and heterogeneous" (p. 2918) and based on surrogate markers of infertility such as amenorrhea.

Table 31.1, adapted from the ASCO recommendations [1], identifies several cancer therapies that are known to almost universally result in sterilization in women. These therapies include conditioning regimens for stem cell transplantation and pelvic external beam radiation. More complicated is assessing the risks of treatment regimens associated with breast cancer treatment on fertility. There are many factors to consider including: dose and combination of agents, patient age at the time cancer treatment begins and ends, duration of treatment (e.g., endocrine therapy with tamoxifen for 5 years), baseline ovarian reserve, and pre-existing infertility. Patient variation in polymorphisms for drug metabolizing enzymes may also be important in determining a drug's effects on ovarian function; research in this area is ongoing [2]. New therapeutic agents are continually being introduced for clinical use with little knowledge of long-term sequelae. Thus, when counseling women with

**Table 31.1** Risk of permanent amenorrhea after chemotherapy and radiotherapy. Adapted from Lee et al. [1]

| Degree of risk | Treatment |
|---|---|
| High risk (>80%) | • Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan<br>• External beam radiation to a field that includes the ovaries<br>• CMF, CEF, CAF × 6 cycles in women age 40 and older |
| Intermediate risk | • CMF, CEF, CAF × 6 cycles in women age 30–39<br>• AC × 4 in women age 40 and older |
| Lower risk (<20%) | • CHOP × 4–6 cycles<br>• CVP<br>• AML therapy (anthracycline/cytarabine)<br>• ALL therapy (multi-agent)<br>• CMF, CEF, CAF × 6 cycles in women age less than 30 |
| Very low or no risk | • Vincristine<br>• Methotrexate<br>• 5-Fluorouracil |
| Unknown effects | • Taxanes<br>• Oxaliplatin<br>• Irinotecan<br>• Monoclonal antibodies<br>• Tyrosine kinase inhibitors |

cancer regarding their risk of treatment-related infertility, it is important not to focus only on her initial cancer diagnosis, but also on her treatment plan and baseline risk factors for infertility. In many cases, the preferred mechanism for this discussion is referral of interested patients to a fertility specialist.

Tracking fertility outcomes after specific treatment regimens in individuals is an important objective in the field of oncofertility. Until better data are available, clinicians need to be cautious when using the limited and incomplete information currently available. After counseling patients about their risks and the flaws in our existing data, it is important for clinicians to offer patients options for dealing with these risks. Referring patients to websites such as those established by the Lance Armstrong Foundation may be helpful, but it is more appropriate to offer interested patients further discussion or referral to someone with expertise in reproductive medicine and assisted reproductive technologies (ART) and more specifically in the management of oncofertility patients.

### Initiating the Discussion of Oncofertility Options

Since effective treatment of the underlying malignancy remains the driving factor in decisions about oncofertility, coordination and communication between the reproductive medicine team and the oncology team are critical. While the oncology team may initiate oncofertility discussion or referral to the reproductive medicine specialist, the primary burden of this ongoing communication usually rests with the reproductive medicine specialist. Collaboration and interaction between these two teams is key to treating patients in a timely fashion and to ensuring that patients receive consistent information regarding the most appropriate intervention given their situation.

The oncofertility treatment options we focus on in this chapter require the use of assisted reproductive technologies (ART) such as embryo banking, oocyte banking, and ovarian tissue banking. Cryopreservation of excess embryos after in vitro fertilization is an established tool in ART. Oocyte banking and ovarian tissue banking are considered experimental and should only be offered or practiced as part of a research protocol under the direction, input, and approval of the appropriate institutional review board [3–5]. Other oncofertility options include ovarian transposition and ovarian suppression with gonadotropin releasing hormone (GnRH) agonists and antagonists. Ovarian transposition has been proven to aid in protecting ovarian function against the harmful effects of pelvic irradiation and can be performed by physicians with appropriate surgical training. Although not proven, some data suggest that GnRH agonists and antagonists may be helpful for women being treated for some types of cancer. Administration of these agents does not require any specialized training.

## *Established Oncofertility Options for Women: Embryo Banking*

Embryo banking prior to cancer treatment has risks that can be predicted from years of experience with embryo cryopreservation in the practice of ART for routine indications. Traditionally, embryo cryopreservation has been used as a means to increase the cumulative live birth rate after in vitro fertilization (IVF) in patients being treated for infertility. Typical IVF treatment begins with gonadotropin stimulation to promote ovarian follicular recruitment. Oocytes are retrieved and fertilized in vitro. The embryos are cultured for a number of days and the best quality embryos are typically transferred, leaving excess embryos to be frozen for future use. With embryo banking, all of the embryos are typically frozen soon after fertilization with little information regarding the embryos' quality.

Embryo banking can take anywhere from 2 to 6 weeks, which may limit the utility of this technique in oncofertility patients with aggressive cancer. Also, because oocytes must be fertilized, we recommend this strategy for patients who have consenting male partners and for women without male partners who are appropriately counseled regarding the use of donor sperm [6]. For women without a partner or who do not want their oocytes to be fertilized, oocyte banking or ovarian tissue cryopreservation may be more appropriate.

While embryo banking may increase the chances a woman will have a genetically related child in the future, there are risks. Many of these risks are outlined in ASRM's guideline titled "Elements to Be Considered in Obtaining Informed Consent for ART" [7], including the risks of adverse reactions to medications, risks associated with oocyte retrieval, and risks that a patient may not respond to medication or have poor oocyte recovery rate. Several additional considerations important to discuss with patients undergoing embryo banking as part of an oncofertility strategy are delineated in ASRM's Ethics Committee statement titled "Fertility Preservation and Reproduction in Cancer Patients" [8]. The most clinically significant of these additional considerations are highlighted below along with others we have found to be important.

## Success of Embryo Cryopreservation: Evidence from the Society for Assisted Reproductive Technology (SART)

As part of the counseling process, we recommend that clinicians discuss success data from the Society for Assisted Reproductive Technology (SART). SART was established in 1985, 7 years after the first IVF baby was born and 2 years after the first baby was born by a frozen embryo transfer (FET). SART publishes success data from more than 85% of ART clinics in the United States practicing in vitro fertilization. Although SART data are not specific to women with cancer undergoing embryo banking, in our practice we routinely refer to SART data (Table 31.2) when counseling cancer patients about their chances of having a live birth after IVF with FET. These data demonstrate that fresh embryos from non-donor oocytes provide better pregnancy rates than frozen embryos. However, with embryo banking, no embryos are transferred in a fresh cycle, potentially leaving better quality embryos for FET. This may lead to higher pregnancy rates than what are seen with traditional FET, but it is important to emphasize that the chances of pregnancy will never be 100%, and they are not likely to be higher than what is seen with fresh embryos.

**Table 31.2** Chances of live birth and multifetal pregnancies in patients included in 2007 data from the Society for Assisted Reproductive Technology [9]

| Type of ART cycle | Patient age | | | | |
|---|---|---|---|---|---|
| *IVF cycles using fresh embryos from non-donor oocytes* | <35 | 35–37 | 38–40 | 41–42 | 43–44 |
| Number of cycles | 38,372 | 21,707 | 19,099 | 8,865 | 5,749 |
| Percentage of cycles resulting in live births | 39.9 | 30.5 | 21.0 | 11.7 | 4.6 |
| Average number of embryos transferred | 2.2 | 2.5 | 2.8 | 3.1 | 3.2 |
| Percentage of live births with twins | 32.9 | 28.4 | 22.0 | 14.9 | 9.1 |
| Percentage of live births with triplets or more | 1.8 | 2.0 | 1.5 | 0.7 | 0.4 |
| *Thawed embryos from non-donor oocytes* | <35 | 35–37 | 38–40 | 41–42 | 43–44 |
| Number of transfers | 9,499 | 4,895 | 3,240 | 1,043 | 652 |
| Percentage of transfers resulting in live births | 34.0 | 30.4 | 25.0 | 20.7 | 14.6 |
| Average number of embryos transferred | 2.2 | 2.2 | 2.3 | 2.6 | 2.5 |

## Unknowns of Embryo Banking for Women with Cancer: Evidence from Embryo Cryopreservation Literature

The SART data demonstrate that although embryo cryopreservation is a proven technology, it is not a guarantee for future fertility. While the techniques used for embryo banking are the same as those used for traditional embryo cryopreservation after IVF, it is important for patients to know there are no existing data specific to the success of embryo banking strategies regarding pregnancy outcomes or regarding safety in women with cancer [10, 11]. Under standard ovarian stimulation protocols, estradiol levels can reach 4,000–5,000 pg/ml unless anti-estrogen medications such as letrozole are used to keep them lower. To date, there is only one published study tracking women with breast cancer who elect ovarian stimulation using a letrozole-containing protocol that shows no increased risk in cancer progression [11]. There are no data on the safety of stimulation protocols without letrozole.

Fully informed patients also need to know that specific embryo transfer practices after embryo banking have not been established. Therefore, clinicians often are guided in their transfer strategies by the ASRM embryo transfer guidelines [12]. The risk of multifetal pregnancy is higher with standard embryo transfer guidelines than it is with natural conception (Table 31.2). When to discuss the risks of multiples and the number of embryos to transfer with these patients are questions that have not been answered. Experience from the traditional IVF population would suggest that the earlier the discussion begins the better the results [13]. Further tracking of patients undergoing embryo banking as a fertility preservation option will provide insight to these unknowns.

When creating and freezing embryos for a cancer patient's future use, unforeseen conflicts may arise [14]. Potential areas of conflict that should be addressed in counseling patients include use of donor sperm [6], disposition of unused embryos [15], and disposition of embryos when relationships change (including divorce or death) [14]. Some of these conflicts are predictable as demonstrated by literature from reproductive medicine's past. Reference to this literature may be helpful in counseling cancer patients [6, 15, 16]. Whether or not these conflicts require answers prior to proceeding with embryo banking is debatable. For legal purposes, documentation of discussions and decisions may be helpful should conflicts arise [14].

Two final explanations patients undergoing embryo banking should receive are that there does not appear to be any increased risk of congenital anomalies to children born from frozen embryos and that length of storage does not appear to be a factor in survival of embryos. However, very little data are available regarding ART offspring. Future studies tracking outcomes of ART offspring are necessary.

## *Experimental Oncofertility Treatments: Oocyte Cryopreservation*

For women without a partner or for whom donor sperm is not an option, oocyte banking may be a suitable oncofertility option. Similar to embryo banking, oocyte banking requires ovarian stimulation with gonadotropins and oocyte retrieval. Oocytes are then cryopreserved. As with embryo banking, the entire process can take from 2 to 6 weeks depending on where the patient is in her menstrual cycle when she begins stimulation treatment. Unlike embryo banking, however, oocyte banking for future fertility is considered experimental, defined by ASRM as an infertility treatment that lacks "adequate scientific evidence of safety and efficacy" from appropriately designed, peer-reviewed published studies by different investigator groups [5, 17]. Despite this status, recent data from Italy, where laws prohibit embryo banking, suggest thawed oocytes can be successful and safe in helping patients achieve a live birth [18]. Both ASRM and the American College of Obstetricians and Gynecologists endorse the promise this technique holds for cancer patients [4, 5]. Until the practice is refined, however, oocyte banking should only be performed in the context of a clinical trial and as research under the guidance of an institutional review board (IRB) [17]. Resources such as Fertile Hope's Cancer and Fertility Referral Guide can help patients and clinicians find centers with IRB-approved oocyte freezing programs [19].

As with embryo banking, oocyte banking may also raise future conflicts for cancer patients. Some of these conflicts are similar to those experienced by patients who have frozen embryos, but others may be unique to patients who elect to freeze oocytes [14]. Patients who freeze embryos can usually have their embryos shipped to any center of their choosing when they are ready to use them. On the other hand, because laboratory protocols for oocyte cryopreservation are not well established, patients may have fewer centers to choose from and may have to return to the center where they had their oocytes initially frozen in order to use them. Also, costs associated with the preparation of frozen oocytes for thaw, fertilization, and transfer may be different than those associated with preparation of frozen embryos [3]. Financial barriers could potentially pose problems for some patients trying to utilize their stored oocytes as fertility treatments are often not covered by insurance [14]. Finally, similar to embryo banking, there does not appear to be any increased risk of congenital anomalies to children born from frozen oocytes, but more follow-up data are needed. Theoretical risks include damage to the meiotic spindle of frozen oocytes that could possibly increase the risk of aneuploidy in embryos resulting after fertilization [18]. More research is needed to determine the importance of these issues and others in counseling women about their oncofertility options.

## *Experimental Oncofertility Treatments: Ovarian Tissue Banking*

For patients who do not have the time required for embryo banking or oocyte banking, ovarian tissue banking may be an option. This technique involves surgical removal of ovarian tissue which is then cryopreserved and banked for future use. As with oocyte banking, ovarian tissue banking is considered experimental and should only be performed in the context of a clinical trial as research under the guidance of the appropriate Institutional Review Board (IRB) [4, 5]. Unlike oocyte banking, however, much less has been published or proven regarding methods for preparation and use of the tissue or the capability to yield fertilizable oocytes and viable offspring. Although there are a handful of published reports of pregnancies and live births occurring after transplantation of thawed ovarian tissue [20–24], we do not know the denominator that was required to achieve those live births. Finally, while very little is known regarding how patients feel about their stored tissue and what they do with it, it is reasonable to expect that patients may face conflicts and challenges regarding their frozen tissue similar to conflicts women face who elect for oocyte cryopreservation (including the potential for a limited number of centers that can help women utilize the frozen tissue) [14].

## *Achieving Informed Consent in the Care of Oncofertility Patients*

Opinions vary about how truly informed consent is achieved [25, 26]. The Nuremburg Code and the Common Rule both provide guidance for achieving informed consent to participate in research. The Nuremburg Code calls for a research subject to "exercise free power of choice," have "sufficient… comprehension," and "sufficient knowledge" to make a decision to participate in research [27]. The Common Rule provides additional guidance to many university IRBs in reviewing research consent processes and documents [28]. In accordance with the

Common Rule, our own university's IRB requires consent documents to be written at an appropriate reading level for participants to understand the reasons for, the methods for, the risks associated with, and the safety precautions in place for the research [25, 28]. These guidance documents – supported by a vast professional literature – emphasize the importance of dialogue between the patient and the person obtaining the consent [25, 27]. In the case of oncofertility, this dialogue should include discussion of the points raised in this chapter.

When considering the necessary components for informed consent in the care of oncofertility patients, we recommend beginning with ASRM practice committee guidelines dealing with ART and oocyte and ovarian tissue cryopreservation [3, 5, 7] and the ASRM Ethics Committee statement on fertility preservation and reproduction in cancer patients [8]. ASRM guidelines exist for counseling and consenting patients regarding ART (including procedures requiring oocyte retrieval and fertilization). ASRM has additional practice committee guidelines that define experimental therapies (including oocyte and embryo banking) and identify the necessary elements for discussing oocyte banking with patients. Some of these guidelines address documentation of disposition decisions for banked embryos, oocytes, and ovarian tissue in the event of a patient's death. These considerations are important for preventing posthumous reproductive decisions that a patient would not have condoned. Documentation of disposition decisions in the event of changing relationships such as divorce is also important to protect patients and their partners. Ultimately, standardized consent documents may be helpful in the care of oncofertility patients as these patients may seek future care in a different facility than where they had their gametes or embryos initially preserved.

Experience from the practice of ART may help guide current counseling and consenting of patients in oncofertility. However, further research is needed to determine the best application of ART techniques in oncofertility and to determine the utility of experimental options. Remaining questions that need to be answered include:

- How can oncofertility care be facilitated for women with newly diagnosed cancer?
- When should oncofertility patients be counseled regarding the costs and procedures that may be associated with processing and use of their banked tissues?
- Do strategies for obtaining gametes or tissue affect cancer outcomes?
- How far should the techniques of preimplantation genetic diagnosis be expanded to reduce the risk of cancer in oncofertility offspring?
- What are the best strategies for obtaining gametes and processing them once patients are ready to use them?
- How should banked tissues be handled in oncofertility patients who die before they can use them?
- How important is it to oncofertility patients to have genetically related offspring, and are alternative options like donor oocytes or adoption equally desirable?
- Should strategies for fertility preservation in women with cancer be expanded to all women?

## Conclusions

Clinicians caring for oncofertility patients bear the responsibility to ensure these patients clearly understand when their treatment options cross the threshold into experimental techniques. Referring to existing guidelines is helpful for achieving consistency in the counseling and consent of oncofertility patients, however, there are many unknowns in the field of oncofertility that can make it difficult to counsel and consent patients about their options. Legal precedents from more routine cases involving banked gametes and embryos provide examples of specific conflicts about which patients may need to be counseled before they consent to oncofertility procedures, addressing some of these unknowns. Collaborative work and research is necessary to answer remaining questions associated with fertility preservation for cancer patients. Such collaboration will eventually help establish evidence-based guidelines specific to oncofertility patients.

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## Chapter 32

# The Fertility-Related Treatment Choices of Cancer Patients: Cancer-Related Infertility and Family Dynamics

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## Introduction

Cancer does not just affect the person battling the disease, but the patient's family as well. Cancer can impact a broad range of family relationships from sexual relations with a partner to how someone parents their child. Family members are also often involved in the treatment decisions that someone with cancer makes, such as showing support for a particular medical decision [1] or even being the primary decision maker [2, 3]. The role that a family member plays in the decision-making process is contingent upon many factors including the age of the patient, their relationship to the cancer patient (e.g., parent vs. child), the patient's own desires [4], prior family dynamics [4, 5], and cultural and community norms [2, 3]. Family members can be involved in many decisions directly related to an individual's cancer battle including which treatment option to choose (e.g., lumpectomy or mastectomy) [6], whether or not to pursue alternative treatments [7], and end-of-life care [8].

Cancer patients also often face secondary health issues stemming from cancer and its treatment that can impact their quality of life post-cancer, such as "chronic pain, cognitive dysfunction, fatigue, peripheral neuropathies, cardiovascular and bone disease, or incontinence" as well as cancer-related infertility (p. 5) [9]. Recently, there has been greater attention paid to such related health issues that can impair an individual's life long after the cancer itself is gone, in part due to higher cancer survival rates today. Today, most people diagnosed cancer will survive and many will have to deal with the potential long-term consequences of cancer such as infertility. However, despite what we know regarding the importance of family relationships as during an individual's battle with cancer, we know much less about how the sequalae of cancer, such as infertility, impacts these family relationships. Moreover, there has been very little research conducted on the role of family members in patient's decisions regarding such secondary health consequences stemming from cancer or its treatment.

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Our aim in this chapter is to broaden our understandings of how cancer impacts an individual's family life by looking directly at how the secondary health issue of cancer-related infertility affects family relationships. Our central research questions in this chapter are as follows:

(1) Which family relationships are impacted by cancer-related infertility?
(2) How does the potential infertility of a cancer patient influence relationships with their family?
(3) What role do family members have in a cancer patient's treatment decisions regarding cancer-related infertility?

We explore these questions by drawing on interviews with 52 younger women who were diagnosed with breast cancer at 40 years of age or younger. Based on our respondents' experiences, we conclude that infertility fears and concerns are a prominent way that family members show social support; but also that cancer-related infertility can places a strain on family relationships. Moreover, we find that a wide-range of familial relationships, including those with partners and parents, are affected by cancer-related infertility. We also conclude that in order to fully understand how women facing cancer make both fertility-conserving treatment choices at the time of diagnosis (e.g., emergency IVF) and later fertility decisions (e.g., whether or not to adopt), the role of family members in these decisions needs to be explicitly examined. Finally, our findings have implications for educational efforts aimed at cancer patients and their families regarding cancer-related infertility.

## Background – Younger Women with Breast Cancer and Cancer-Related Infertility

Although breast cancer is usually thought of as a disease that afflicts older women, 7% of women with breast cancer are diagnosed before 40 years of age and breast cancer accounts for more than 40% of cancers in women 40 years of age and below [10]. Younger women also often face a different prognosis than older women diagnosed with breast cancer. Younger women often develop more aggressive forms of breast cancer, respond less well to treatment, have higher rates of recurrence than their older counterparts [11], and have lower survival rates [10]. Moreover, younger women facing breast cancer may be affected by cancer-related infertility. Cancers and cancer treatments vary in their impact on a patient's future fertility. While some cancer and cancer treatments may pose very little risk to one's fertility, younger women with breast cancer are considered in general to be at risk for impaired fertility. However, the risk varies across patients depending on many factors, including the treatment regimen followed (e.g., choice of chemotherapeutics), the presence of a BRCA mutation, the patient's age, and the patient's baseline ovarian reserve [12]. Both qualitative and quantitative studies on younger women with breast cancer (along with research on cancer survivors of child-bearing age more generally) have found that issues regarding potential infertility are among their top concerns (See [13] for a comprehensive review of research in this area).

Those with cancer can take steps to help ensure that their future fertility capacity is preserved. Most experts agree that patients have the most effective options for fertility conservation prior to the beginning of treatment because of the potentially damaging effects of treatment (e.g., radiation and chemotherapy). Women with breast cancer have several options available depending on their future family goals and particular prognosis (including the stage of the disease at diagnosis, whether or not their breast cancer is hormone receptor-positive, or if the patient has a BRCA mutation) [12]. Prior to treatment, options range from egg/embryo harvesting to more investigational treatments such as ovarian tissue cryopreservation [12]. In addition to these fertility-conserving treatment options, cancer patients may also choose to become parents through alternative routes using donor eggs, surrogacy, and adoption (for a complete discussion of the options available to those diagnosed with breast cancer, see [12]).

Despite clear indications that fertility is a major concern for younger people facing a cancer diagnosis, the topic is not routinely discussed during the diagnosis or early treatment phases. A consistent finding is that many cancer patients, male, female, adult, and child patients, do not recall having any conversation with a physician prior to treatment regarding potential fertility impairment or treatment options. In their review of research on the topic, Lee et al. [14] conclude that "recent surveys of male and female cancer survivors of reproductive age concur that at least half have no memory of a discussion of fertility at the time of their treatment disposition" (p. 2926) [14]. They also conclude that, "Even when patients do recall infertility discussions, many are dissatisfied with the quality and information provided" (p. 2926) [14].

Clearly, research indicates that not all women with breast cancer will have the opportunity to decide on a fertility-conserving treatment plan before cancer treatment begins, but many will contemplate whether or not to undergo such procedures. Many cancer patients will make other fertility-related decisions after their primary treatment has been completed, such as whether or not they should try to have another child or if they will pursue other options such as foster parenting or adoption. However, a significant aspect of family planning not present in current research is how such decisions are made within distinct social settings, particularly in the context of family relationships. In this chapter, we look at the potential influence and role of family members in the fertility-related decisions of cancer patients. By doing so, we also address another issue that has been missing in research on cancer and family relationships: how does cancer-related infertility impact family relationships?

## Methods

### *Sample Recruitment*

The data for this chapter come from in-depth interviews with 52 women who were diagnosed with breast cancer at 40 years of age or younger. Respondents were solicited through recruitment advertisements distributed by healthcare, advocacy, charitable, and support group organizations aimed at those with breast cancer. Organizations that agreed to help recruit for this study typically sent a recruitment advertisement through an e-newsletter/e-mail list or one was posted to a message/discussion board. Fliers were also posted in public spaces by several organizations where clients physically come in for treatment and support services.

## *Sample Characteristics*

Table 32.1 presents an overview of our sample. At the time of their interviews, the mean age of respondents was 34.8 years and the average age of the respondents for their first breast cancer diagnosis was 32.4 (four women in our study were diagnosed with breast cancer twice). Within the past 3 years, 82.7% of respondents were diagnosed , with many still actively receiving treatments, such as chemotherapy and radiation at the time of their interview. All of the women in the study are still within the 5-year recurrence window with most still receiving some type of follow-up care. Additionally, 61.5% of the women are currently married/partnered with an additional 9.6% engaged to be married. Further, 40.4% of the respondents have

**Table 32.1** Overview of respondents

| Sample characteristics ($n = 52$) | |
|---|---|
| *Race/Ethnicity* | |
| Caucasian, Non-Hispanic | 80.8% |
| Caucasian, Hispanic | 5.8% |
| African-American | 9.6% |
| Asian | 3.8% |
| *Educational attainment* | |
| With Bachelor's degree or higher | 86.5% |
| *Family status* | |
| Married/Partnered[a] | 61.5% |
| Engaged to be married | 9.6% |
| With children[b] | 40.4% |
| *Mean age at time of interview (years)* | 34.8 |
| *Mean age at time of first diagnosis (years)* | 32.4 |
| *Age range at time of first diagnosis (years)* | 23–39 |
| *Time since most recent diagnosis* | |
| Less than 3 years | 82.7% |
| 4–5 years | 17.3% |
| With health insurance | 98.0% |

[a] Partnered includes those women who are not legally married but consider themselves to be in permanent partnerships.

[b] This category indicates women who identify themselves as a parent. Although the overwhelming majority of women have biological children, this category also includes non-biological children including foster and stepchildren.

children. Table 32.1 also shows that our sample is highly educated (86.5% have at least a Bachelor's degree), with most respondents having professional or white-collar jobs. Most of the respondents are Caucasian, non-Hispanic (80.8%) and all but one respondent has health insurance.

## *Interview Procedures and Data Analysis*

Semi-structured phone interviews were conducted with respondents. Prior to the interview, respondents were read an IRB-approved statement of informed consent before agreeing to participate in the study. Interview topics included initial diagnosis experiences, family background, treatment concerns and decisions, available support networks, and the impact of a diagnosis on future family plans and their personal relationships. The interview schedule remained flexible – a respondent's responses drove the interviewing process in order to accommodate their unique experiences and perspectives. Interviews averaged 60 min.

We used a grounded theory approach to the data [15], where we did not initiate our analysis with preconceived notions regarding how cancer-related infertility would affect our respondents' family relationships or which family relationships would be impacted. Interviews were first coded by identifying instances where cancer-related infertility was part of a relationship that a respondent had with a particular family member.[1] Sometimes cancer-related infertility was part of a specific discussion between a respondent and a family member and sometimes it was an ongoing topic between a respondent and a particular family member. After identifying incidents and relationships that involved cancer-related infertility, these incidents/relationships were categorized as being supportive or stressful (the latter indicating that the incident/relationship caused the respondent distress or feelings of guilt).

Lastly, we identified instances where family members were directly or indirectly involved in fertility-related decisions. We looked specifically at fertility-conserving treatment decisions that a respondent made prior to cancer treatment (such as whether or not to freeze embryos/oocytes) and how/which family member was involved in these decisions. Since most of our respondents are still within the 5-year reoccurrence window (with most being within 3 years of diagnosis), most have only contemplated post-cancer options of whether or not to try to conceive naturally or whether or not to adopt. In terms of these types of post-cancer decisions, we identified how/with which family members they have started to discuss such issues.

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[1] We only focus here on interactions with adult family members. Many women (41.5%) in our study had children and their cancer diagnosis and treatment had definitely impacted their interactions with their children; for example, respondents expressed concerns about the amount of time they were able to spend with their young children. However, we focus here on adult family member relationships because none of our respondents described discussing fertility-related issues with their children.

## Findings – The Interplay Between Infertility and Family Relationships

Women in this study varied in what their future family plans were. Some wanted to become first-time parents of biological children (with several being pregnant at the time of their diagnosis); some were focused on their career and had not thought about starting a family yet or did not want to become a biological parent ever; and some already had children and were not interested in additional children. Despite this variation in fertility plans, family relationships were key to their diagnostic, treatment, and early survivorship experiences. Moreover, for the overwhelmingly majority of our respondents, cancer-related infertility was, to some degree, an issue that became part of their relationships with their family members.

### *Who Is Your family?*

To understand how cancer-related infertility affects familial relationships, we first needed to understand what the category "family" meant to our respondents. Although respondents were asked during their interviews about how specific groups (namely partner, parents, and children) were involved in their cancer experiences, most questions spoke in terms of "family" very generally. This approach allowed the respondent to create a definition of who is, in fact, their family and what family members were part of their cancer experiences and treatment decisions (general treatment decisions and decisions specifically related to fertility). Among the sample, two distinct definitions of family arose as age and relationship status varied. For those who were younger and/or not in committed partner relationships, "their family" most commonly meant their family of origin, or parents, and to a somewhat less extent, siblings. For example, Katrina,[2] a 33-year-old marketing specialist diagnosed a year and a half ago, is single with no children. She defines her family support network in terms of parents and siblings:

Interviewer: So who would did you turn to for support during your diagnosis?
Katrina: My friends and my family.
Interviewer: Which family members exactly?
Katrina: My parents and my siblings.

Alternatively, married or partnered women were more likely to respond to questions regarding "their family" by focusing more on their relationship with their partner or spouse. For example, Cora, a 31-year-old married television writer, was diagnosed 2 years ago with breast cancer. Although she mentions other family

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[2] All names are pseudonyms.

members throughout her interview as influential in her cancer experiences, it is her husband that she sees as her primary family support system:

Interviewer: So who would did you turn to for support during your diagnosis?
Cora: My husband, my close friends, my family.... my husband was the number one go-to-person.

In recent decades, the transition to adulthood has changed considerably with increasing delays in the age of first marriage and parenthood and a longer and varied path to establishing careers and completing education [16]. This means that younger adults today are far from a cohesive group, but rather include those at very different lifestyle and family stages. For our sample, this means a range in how they defined what "family" meant to them and which family members could potentially be involved in how a younger woman facing cancer approaches fertility-related decisions.

## *Infertility Concerns – Shows of Familial Support*

Respondents in our study described their family members as being their central support systems throughout their diagnosis, treatment, and transition to survivorship. Respondents discussed how their family members provided emotional support and helped with necessary daily tasks including assisting with childcare and looking up information on the Internet. What was striking when respondents recounted instances of social support from family members was how often the issue of fertility was central to these shows of emotional support. Although survival was clearly the main issue for all of the women and their families and not all women were concerned about their ability to have children in the future, family members often helped cancer patients come to terms with their fertility-related concerns and the topic of infertility was a primary issue that our respondents and their families discussed.

Some women even felt that their cancer and potential infertility had enhanced their relationships with partners and spouses because of the depths of support their partners displayed. Infertility concerns became a venue to talk about their future plans together and their commitment to one another. Ennette, a 28-year-old married corporate event planner, had always wanted children growing up. Upon hearing that her cancer may prevent her from having biological children in the future, Ennette was upset:

> I had really hard time with it. I think I was extremely frustrated that my original plan for my life wasn't working out the way I thought it would and it was extremely difficult to I guess mourn children that I never had and the possibility that I might never have them. I think I was really upset at the fact that cancer was kind of – it was affecting another part of my life like kind of like a casualty. That otherwise I was healthy and didn't have any fertility problems.

Despite feeling that her and her husband's life's plans had been derailed, Ennette also believes the potential of infertility has brought her and her husband closer:

Interviewer: How has your relationship with your husband been affected?

Ennette: I think we've become closer. I think that we talk about the future more. It's been affected in a positive way, I think.

Kathy, a 36-year-old married physician, discussed how the potential of not being able to have biological children was a common topic of conversation between her and her husband. Kathy characterizes their relationship and their commitment to becoming parents as being very supportive: "Well he's been really supportive so that's been good. I mean it's stressful. I think, you know, he's felt bad for me. But I think he knows we'll do whatever we need to do to have a family still. I think it's been stressful, but I mean we're very supportive of each other." Like Ennette, she also feels that her cancer and potential infertility has brought them closer together, "I mean it's stressful, but we're very close. We're closer than we would have been if we hadn't been through all of this."

Parental shows of support also commonly involved fertility issues. Susan, a 29-year-old married occupational therapist, was diagnosed with breast cancer at 25 years of age. Susan and her husband would like to have their first child, but because she does not know if her fertility has been impaired due to her chemotherapy treatments, this issue is a source of concern for her: "It makes me feel – it makes me feel a little anxious, especially given that many of my girlfriends are having children right now. But I just have to wait. You know? I'm not done with my Tamoxifen yet. But I don't think that – or wish I would have done anything differently. You know? It is what it is."

At the time of her treatment, Susan's primary confidant regarding her fertility concerns was her mother since she and her husband were not yet married. Susan described her parents as being extremely supportive during her diagnosis and treatment; also, despite the fact that she knows her parents would like to have grandchildren, she does not feel any pressure from them to have children and appreciates their understanding: "I think regardless of what happens, if we decide we don't want to have kids, or we do have children, they'll be supportive no matter what. There's no pressure, at all, from them to have children."

When our respondents discussed how supportive their parents and partners had been throughout their diagnosis and treatment, fertility issues were central to many of their family's shows of support and heart-to-heart talks. Other family members also indicated their support as well in regards to respondents' concerns over their future ability to have additional biological children, including discussing the topic with siblings. Daniela, a 37-year-old married mother of one, even had both her younger sister and her sister-in-law offer to carry a child for her if she needed a surrogate down the road.

## *Potential Infertility and Family Relationship Stress*

Although the focus in much research on cancer has looked at how family support (or lack thereof) can be related to a particular health outcome, researchers have begun to consider how intimate relationships can be a source of tension as well as (e.g., [5, 17]). Among our respondents, families could be a source of tension as well as support. In particular, issues regarding fertility were often an impetus for the strained relationships with family members. Tamara, a 36-year-old married occupational therapist, terminated her first pregnancy when she was diagnosed with breast cancer. She and her husband, Matthew, then delayed her cancer treatment to do emergency IVF. She then had her uterus removed because her cancer was BRCA positive. Tamara and Matthew are planning on using the banked embryos to have biological children later on through the use of a surrogate. Tamara describes her relationship with Matthew as being generally very supportive including him supporting her decision to undergo IVF. Tamara, however, also feels bad because of the impact that her infertility has had on Matthew: “Well, you know, it’s been horrible for him because his option of having a child of his own, may have essentially been taken away . . . So that’s been absolutely devastating for him.”

Further, she describes feeling of guilt regarding what may happen to their family plans because of her breast cancer:

> My first overriding feeling when all of this happened was guilt. Very guilty for taking away the fertility options from my husband. Very much internalized that. And anger and the feeling of sort of things not being fair, or a little bit hopelessness. That now the option has been potentially taken away from us. And anger, I think anger more because as you’ll find out, as I’m sure you’ll ask me more questions, I have the BRCA gene, but I was not aware of the family history until after I was diagnosed as much. I knew about one, but not all. So had I known, we would not have put off our family plans as long as we did. So there was anger about that.

Kristen, a married 27-year-old chemical engineer, does not have children. It is unclear if her ability to have children has been compromised from her cancer treatments. However, she often worries about what will happen if she and her husband are not able to conceive naturally because they had always talked about having children before they turned thirty: “It kind of knocks you off the path that you were on and it has an impact on your relationship. . . . I don’t know. I just felt like I, you know, I couldn’t give him what he would want from me. He wanted to have a child too, so it kind of just made me feel like I couldn’t provide for him what he wanted.”

Although Kristen describes her husband as generally supportive, the stress of her illness and the possibility of not being able to have a child together have caused them at times to take out their frustrations on one another. According to her, “It constantly seemed like we were so angry and we kind of were taking it out on each other.” Kristen says they are now trying to work through these issues and have considered adoption if they are unable to have biological children.

What was even more notable among our respondents’ narratives was how often parental relationships were a source of stress regarding their ability and plans to have future children. In fact, parental relationships were mentioned as much, if not more, than partner relationships as being a source of tension and strain. Anna, a 40-year-old divorced teacher with no children, believes her possible inability to have children in the future is a source of disappointment for her parents:

> Oh, yes. They would love to have grandchildren . . . neither one of my sisters have children either. I would love to have given my parents grandchildren. They would have been great grandparents . . . I know that my mom has mourned with me that she doesn't have grandchildren . . . And my dad hasn't, as much, expressed a desire for grandchildren, but I know he's – he just doesn't talk about it as much, but that would be something he wanted.

Though Anna expresses that this issue is one that deeply affects her parents, she does not describe the situation as being contentious between her parents and herself. Rather, it is another source of concern and sadness for Anna as she copes with her illness.

However, some women expressed that this issue has in fact caused outright tension in their relationships with their parents. LaTisha, a single 32-year-old Ph.D. student, had lymphoma as a child in addition to her breast cancer. She describes having a strict Protestant upbringing where it was assumed that, as most of her relatives had done, she desired to be a young mother and would have children. LaTisha feels her relationship with her mother is strained in part due to her mother's desire for her to have children:

> It's been not great. Like I said, I have an older brother and he didn't have any of his own children. His wife has a child from when she was married before and so there was already this pressure on me to be the one that's going to carry on the family line. And then cancer, I think, just made it – heightened it, because I mean there was still the expectation that I was going to have a kid, but then there was the understanding that it may be that much difficult, but it's worth the effort to have the kid. So, yeah, it's been – I've talked to my mom some about not bringing it up as much and she says she doesn't bring it up as much, but she does it – she actually does, just in a different way. She talks about, my mom was a twin sister, so she'll talk about her twin sister's grandkids and, oh, wasn't it great, you know, and, oh, I wish, you know, I saw them do this and it's her own jealousy of not having her own grandkids, but she kind of projects it on to me.

This tension or concern stemming from parental relationships can also have the opposite effect where parents voice their desire for their daughter *not* to have biological children in the future because of the fear that a pregnancy may not be safe. Donalyn's (34-years-old, married, no children) parents have made their concerns known about her potentially using an egg donor so that she and her husband can conceive their first child:

> They don't want me to become an egg donor recipient because they feel that – and they feel that me getting pregnant on my own would make my cancer come back just because of all the estrogen and progesterone. They're kind of nervous about me becoming pregnant, with the fear of having my cancer come back.

Ellen, a 26-year-old engaged mother of one child, also describes how the topic of her having additional children has caused tension within her family – her stepmother had made several *nasty* comments about how her becoming pregnant may not be possible or potentially risky due to her history of cancer.

## *Family Influence and Fertility-Related Decisions*

Fertility was a not a side issue or distant concern for the women in our study as they went through treatment and made the transition to being a cancer survivor. For most in our study, it was their top concern aside from their own survival. Their fears over infertility and the uncertainty about being able to have children in the future was an opportunity for family members to show support or for otherwise close relationships to be strained. The interplay between family relationships and cancer-related infertility concerns among our respondents' experiences indicates that those who are interested in how cancer patients make fertility-related decisions (both decisions at the time of diagnosis/treatment such as whether or not to pursue IVF and those post-cancer such as whether or not to adopt) should examine how such decisions are made in the context of familial relationships. Our respondents' experiences show how both supportive and stressful family relationships can shape their decisions regarding their fertility and future parenting plans.

As discussed above, research has consistently found that patients are not always told about fertility impairment during their cancer diagnosis or treatment. Some of our respondents knew of potential fertility impairment and treatment options before undergoing treatment and others only learned about the potential after their treatment had ended. But despite this variation in when they learned about the issue (and whether or not they were even interested in having any or additional children in the first place), what is clear from our study is that a wide range of family members, most notably parents and partners, feel invested in the fertility-related choices an individual with cancer makes.

When faced with whether or not to pursue fertility preservation prior to treatment, most partnered respondents describe their spouse/partner as being the person they primarily made the decision with. For example, Julia, a 32-year-old married researcher, had a child after her cancer treatment had ended. She had contemplated doing emergency IVF prior to her chemo, but ultimately decided against it – her husband was part of her decision-making process:

Interviewer: Did you contemplate having these procedures done?

Janet: We did, but initially, to harvest the eggs, it would have taken too long and we wanted to start treatment right away. And, ultimately, we wouldn't have needed it anyway.

Interviewer: What did you see as the risks and benefits of emergency IVF?

Janet: The risk of the cancer was greater than the benefits of having that happen.

Interviewer: How did you decide?

Janet: Discussions with my husband.

Interviewer: Can you elaborate a little bit on that?

Janet: Well we just we talked about the possibility of doing the IVF and from the feedback that we had got from the doctor that he had had patients recover completely from chemotherapy; we decided that we would just chance our ability to conceive later.

Janet describes a decision-making process where she and her husband are a team where "we" had decided how to proceed. Other women describe themselves as the primary decision-maker in terms of their fertility-conserving treatment decisions with their partner's primary role as being supportive of their decisions. Allison, a 28-year-old married mother of one child, decided to delay treatment to do emergency IVF. She describes the decision as hers, with her husband being supportive of whatever she wanted to do:

Interviewer: And how did you decide to undergo this procedure? Who was involved in the decision?

Angie: It was mainly me. I mean my husband was behind me 100%, and he told me whatever I wanted to do, he was comfortable with. But, again, it was just peace of mind, getting that finished and knowing that they would be there after all that is finished.

But even if partners were the central person in the decision to pursue fertility preservation, parents' reactions and support was often still important. Ennette, discussed above, decided along with her husband to delay treatment and undergo IVF. Her parents' approval of this decision helped her feel comfortable and supported:

Ennette: Yes. They were very supportive of my decision to move forward with IVF.

Interviewer: How do you think this affected you?

Ennette: It just made me feel more confident in my decision and I think I didn't feel as alone.

When most of the women in our study mentioned the role of parents in their decision-making regarding fertility, their influence seemed to be less direct, albeit still influential, as in the case with Ennette, who primarily made the decision with her husband. However, there were some instances of parents being directly involved. For Idelle, a single 39-year-old with no children who works in business development, her parents played a very direct role in her decision to go ahead with oocyte harvesting. Although she describes her relationship with her parents as good, her parents have always placed pressure on her to have children: "When they hit a certain age and their parents constantly say, 'We want a grandchild like all of our friends.'"

In order to help ensure that they had grandchildren, her father was very proactive in encouraging Idelle to undergo oocyte harvesting:

Idelle: I did. I harvested eggs. So I did IVF and harvested eggs which now are in the freezer.

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Interviewer: How did you decide? Who was involved in the decision?

Idelle: Me and my father, only because he paid for the whole thing.

Interviewer: How did you decide?

Idelle: Dad said, "Here's the credit card, go get it. I want to make sure I'll have insurance on a grandchild."

Family influences are also apparent as our respondents discuss whether or not they would pursue alternative routes in the future to become a parent. Since most of our respondents are only within a few months to a few years post-treatment, most see the decision of whether or not to try conceive naturally or become a parent through other means as issues they will decide in the future; however, many have already begun to discuss their future options with partners. Patricia, a 39-year-old married mother of one and a writer, is content with having only having one child, but has raised the issue of adoption with her husband:

Patricia: We've kind of mentioned it, or I've kind of mentioned it. He's not quite so sure about that. So just the fears of the risk of losing the child, the parents wanting it back or whatever. And I know some people who have been through adoptions and they are very – they're tricky. They're really emotional.

Megan is 38-years-old, has been married for a year, and she and her husband hope to have children someday. She was not aware that there were options, such as emergency IVF, prior to undergoing chemotherapy and is unsure of her current fertility status. She and her husband are also unsure if she should actually try to conceive in the future, but they have extensively discussed other options:

Megan: Well, for me personally, I don't think I have to give birth for it to be part of my family and I think both adoption and foster parenting would be great. I still think that it creates a family and I'm fine with that.
Interviewer: Would you consider surrogacy?
Megan: We have discussed surrogacy. So, yes, I guess we have – we are considering it.
Interviewer: And why are you considering it?
Megan: It would be an opportunity for the child to be part of my husband.

Respondents were most likely to discuss issues such as adoption or surrogacy in the context of their partner/spousal relationships, but parents' opinions could still be influential. And some parents have even suggested that respondents adopt. In fact, Jasmine, a 31-year-old with no children and a long-term partner, would prefer to try to have her own child, but is waiting to be past her 5-year reoccurrence window. However, her mother has already pushed the topic of adoption even though Jasmine had let her know her parenting plans: "She wants grandchildren and I think she was, earlier on, talking about adopting while I was in my 5 year waiting time when I'm on ovarian suppression."

Although parents and partners were often discussed as primary confidants in regards to fertility concerns and plans, other family members could also be involved in discussions regarding options such as adoption. LaTisha, discussed above, whose mother has put much pressure on her to become a mother, has considered becoming a foster/adoptive parent and has turned to family members, such as her aunt who is also a breast cancer survivor, to discuss the topic:

Interviewer: Would you consider adoption or foster parenting?

LaTisha: Yes. I have foster parents in my extended family. My aunt is a foster parent and I've talked to her, and she's also a breast cancer survivor. But she was a foster parent first. And so I've talked to her some about that and also sort of looked into adoption organizations that are friendly to cancer survivors.

## Conclusion

A limit of our study is that our sample is homogenous in terms of race/ethnicity and socioeconomic status. A more diverse sample is needed to more fully understand how younger women with breast cancer experience cancer-related infertility in the context of their family relationships since cultural norms regarding who is involved in medical decisions, the importance of having children, and how individuals interact with healthcare workers can vary by cultural group. Nonetheless, our study shows that cancer-related infertility impacts more than just the cancer patient – relationships with her partner and with her parents are also affected – and any fertility-related decisions are made within the context of these supportive and stressful family relationships. Future research on medical decision-making in terms of cancer more generally should expand on the growing body of research that examines how disagreements and strain among family members and relationships can ultimately shape treatment choices [5, 18].

Our research also has implications for the increasing number of resources for cancer patients on the topic of fertility. Many websites that are aimed toward adult cancer patients have resources regarding infertility for partners. Additional materials regarding infertility that are directed toward parents of adult cancer patients may also be beneficial. The goal of these resources is not for parents to encourage or discourage certain options for their sons and daughters, but to provide parents with the means to understand the issues. Since many of the women in our study, particularly those who did not have a long-term partner or spouse, said they most leaned on their parents for support, information geared toward the parents of adult cancer patients may be valuable. Recognizing that parents may be the primary support team of adult cancer patients can help to ensure that valuable treatment and fertility information is not overlooked by being placed under headings and labels that indicate "for partners/spouses" only.

There are also support and educational resources aimed at family members who have a loved one going through cancer. Based on the reported involvement of respondents' partners and parents regarding fertility concerns and decisions, such support and educational resources should recognize very directly that part of coping with a family member's cancer may involve mourning one's own life's plans and goals, which may involve having additional or first-time children and grandchildren. Moreover, research that directly examines family members of cancer patients is needed in order to have a greater understanding of how family members experience and cope with a cancer patient's potential infertility.

The suggestions above are meant not only to help family members navigate and come to terms with a cancer patient's diagnosis and potential fertility impairment but also to design pathways to help a patient make the best decisions for themselves. The experiences of Ennette and others in our study clearly show that how confidently fertility-related decisions are made can hinge on how family members, such as parents and partners, react to and support such decisions. Moreover, research has shown that patients who are comfortable with their treatment decisions and their role in the decision-making process can have better health and emotional outcomes [19, 20]. For example, Lantz et al. found that when breast cancer patients' preferences for their involvement in treatment decisions matched their experiences (e.g., not being under or over-involved), they were more satisfied with the treatment process and outcomes and experienced less regret/ambivalence [20]. Therefore, patients who are happy with the fertility-related treatment choices they make, how they arrived at those decisions, and feel supported by their families may experience positive consequences (e.g., greater satisfaction) beyond whether or not they are able to have children in the future. Our suggestions above are not meant to push adult patients into making decisions that are best for their parent or their spouse; rather, our aim is to provide information to those who are already part of and influential in these decisions in order to help patients best communicate their needs, wants, options, and ultimate decisions.

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# Chapter 33
# Whose Future Is It? Ethical Family Decision Making About Daughters' Treatment in the Oncofertility Context

**Kathleen M. Galvin and Marla L. Clayman**

## Introduction

In cases of fertility-threatening cancer treatments, the choice whether or not to undergo fertility preservation treatment before cancer treatment begins represents a high-stakes, time-sensitive, emotionally charged, nested decision [1]. The choice is life altering and, although presumably a discrete decision, the fertility preservation decision serves as an outcome of a very recent challenging decision to pursue fertility-threatening cancer treatments. Patients and their family members will experience the dual impact of these linked treatment-related decisions for years to come. For many patients, family members play significant roles in treatment-related decision making. However, if the patient has not reached the age of legal majority, family members play additional roles in the decision-making processes. Multiple issues confound the fertility-focused decision involving female children and adolescents; such complicated and critical family-related medical decisions raise multiple underexplored ethical concerns.

This chapter addresses a range of family factors and related ethical issues that affect decision making when a female child or adolescent is faced with fertility-threatening cancer treatments. Following the presentation of a framework through which to examine the role of children in decision making, several child- and family-oriented complications related to both ethics and family communication will be explored. The focus of this chapter is on girls because the current oncofertility options for prepubescent and adolescent girls are more invasive and less predictable than they would be for an adolescent male considering sperm banking to achieve future biological parenthood.

This exploration reflects a family systems' perspective, best captured by Minuchin's [2] claim, "Decontexted individuals do not exist" [2, p. 2]. From this perspective, individual family members are considered as parts of a family system

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and its interaction patterns; a change affecting one member of the family reverberate through the entire system. Communication is central to understanding these family system patterns and their changes [3] because decisions made by one or more members impact all members to the extent that they are connected. The American Academy of Pediatrics (AAP) states that effective communication "is essential to patient-centered and family-centered care" [4, p. e1441]. In addition, factors related to the family's background and experiences (be they cultural, socioeconomic, or religious) affect the decision making by family members as individuals and as a unit.

## Ethical Consent and Children

Traditionally, parents have assumed responsibility for making medical decisions for their children's care, even if that has meant choosing to allow a doctor to decide for them. But, in recent decades, the extent to which children and adolescents should be involved in medical decision making related to their treatment has emerged as an important issue. The prevailing spirit underlying historical parental control is "that parents are the most motivated and capable people to act in their children's best interests, that they often have similar interests to their children, and they are more competent to make medical decisions" [5, p. 507]. However, as there has been a transformation in how American society views the role of the adult patient [6], there has been a similar shift in how child involvement in decision making is conceptualized. The prevailing view today seems to be that children should be involved to the extent possible, given their prior experiences, maturity level, and cognitive and emotional capabilities [4, 5, 7]. In practice, this is difficult to implement with confidence, as every child, family, and clinical situation present unique challenges.

Clinical psychologist Mary Ann McCabe (1996) argues that "we need to support minors' involvement in decision making, particularly for treatment decisions where the clarity of the 'right choice' fades, where treatment preferences are based upon the personal values and 'quality of life' issues" [5, p. 506]. Therefore, "in medical situations where the 'correct choice' is not clear, the adolescent should be invited to have more involvement and his/her own values should be brought to bear on treatment choices" [8, p. 320]. This focus on clinical equipoise (i.e., where there is no evidence for preferring one medical option above another) is in keeping with shared decision making. Although most frequently applied to the adult setting, this approach that advocates for patient involvement in care and an explication of the patient's personal values and preferences [9–11] is also relevant to children.

The American Academy of Pediatrics has several position papers directly relevant to the issues at hand [4, 7, 12]. Currently, the AAP is clear that "[t]here is a moral and ethical obligation to discuss health and illness with the child patient." [4, p. e1445]. The Academy further states that older children and adolescents should have "a significant role" when there is no clearly superior option from a medical standpoint. A model of decision making in pediatric oncology recently introduced by Whitney and colleagues takes this further by attempting to delineate under which circumstances a child, parent, or clinician should have decisional authority [13]. Although deciding whether to initiate cancer treatment, and which treatment to support, may require heavy reliance on the professional's knowledge and perspective, fertility preservation reflects a quality of life decision or personal value approach that the parents and child might address together, assuming a child is able to comprehend the issues.

## The Family Rule Approach

In his widely cited article on obtaining ethical consent for medical interventions involving children, Foreman (1999) argues that "informed consent in children should be regarded as shared between children and their families, the balance being determined by implicit, developmentally based negotiations between child and parent – a 'family rule' for consent." [14, p. 491]. Although his writing relies on the British legal tradition, the issues raised provide a valuable grounding for considering the ethical issues within a health and family communication framework. As we address ethical issues, we will consider Foreman's guidelines and conditions from a communication perspective rather than a legalistic perspective.

After addressing the binds inherent in children's assent and parental consent, Foreman distinguishes between consenting to an *event* (e.g., an action, such as a procedure) and consenting to a *rule* (e.g., agreement to follow a set of prescriptions and prohibitions that regulate conduct) before arguing that "the most important rule children consent to is that of their family" (p. 493). He makes the case that children *implicitly* consent to a family rule thereby agreeing to "follow a set of prescriptions and prohibitions that regulate one's general conduct" (p. 492) and claims that this family rule must promote the welfare of the child and must not be viewed as an all-or-nothing arrangement because developmental factors require ongoing renegotiation of the rule's application until the child reaches adulthood.

In an attempt to provide guidelines for medical practitioners, Foreman proposes a five-step process for ensuring the child has enough information needed to give rational consent (See Table 33.1). In addition, he identifies five conditions that medical practitioners may encounter as they attempt to balance respect for the autonomy of the child as well as respect for the variable (diffuse) nature of a child's right to consent (See Table 33.2). Issues such as age, maturity, and a child's cognitive or

**Table 33.1** Steps for ensuring a child has enough information needed to give rational consent (adapted from Foreman [1, 4])

1. Inform the child of what will happen if nothing is done
2. Describe the intervention
3. Explain how this intervention will improve the situation
4. Ask the child whether or not he or she agrees that this intervention produces a better outcome than the alternative – doing nothing
5. Seeking the child's consent to initiate the intervention

**Table 33.2** Four of Foreman's five situations for child and family decision making[a]

| | Family rule | |
|---|---|---|
| Consent | Child agrees | Child does not agree |
| Child can consent | Agreement | Child's wishes should be respected |
| Child cannot consent | Parents decide; child must be informed | Healthcare team may broker an understanding between the parties |

[a] The fifth situation is an extreme one in which the parents do not have the child's best interests in mind.

emotional state influence a child's decision-making capacity. Medical decision making for a child ideally includes active family communication among the involved parties. Foreman's conditions are based primarily on whether or not the child can provide consent and whether or not the child consents to the family rule.

In the first of Foreman's five conditions, there is the option for joint parent/child decisions and necessitates full medical explanation to both parties. This situation supports open and detailed discussion between a child and parents as they move toward a joint decision. When the child cannot provide fully informed consent, medical practitioners must give a full explanation to the parents and limited information to the child. Importantly, Foreman asserts that *just giving the information to the parent does not ensure the child receives sufficient information*. Therefore, this position implies that parents and a child may hold conversations, but that the burden is on the medical professional to ensure that certain information is conveyed to the child at his or her level of understanding about the future implications. In some instances, this may be at odds with the AAP's position paper on communication with children and families [4]. This document states that the parents and the pediatricians should discuss how to involve the child in decision making. Regardless of which model is followed, the clinician must ensure that the child has an understanding commensurate with his or her capacity. That is, one could argue for ethical decision making if the parents inform the child or if the clinician does the informing, as long as the provider is satisfied that the transfer of knowledge was both adequate and adequately understood.

The remaining situations are more problematic. In the third situation, a child is capable of giving informed consent, but does not consent to the family rule. If the child truly can consent, then the child's desire must be respected [4, 14, 15]. As adolescence is a time of questioning and increasing intellectual and emotional independence, such a scenario is easily contemplated. For example, this might involve a 16-year-old with strong religious beliefs different from her parents. In such cases, family communication is likely to be painful, complicated, and even fractious. In some situations, it may be preferable for the healthcare provider to consider overriding the parents' wishes. This could detrimentally affect the parent/healthcare provider relationship. In these situations, the healthcare provider has an obligation to become the child's advocate [7].

A situation may arise in which the child cannot give informed consent and does not consent to the family rule. Examples include a child misjudging his or her capabilities, believing that expressing individuality trumps a rational approach, or continuing a pattern of rebellious disagreement while expecting to be overruled. This is challenging for two main reasons. First, even adults do not make decisions entirely rationally. It is not reasonable to expect a child to decide based on rational thought when an adult in the same situation would not be expected to act rationally. Ladd and Forman argue that adolescents make choices according to values that they hold precisely because they are developmentally appropriate (and would not necessarily be so in adulthood) [15]. Second, it may be difficult to distinguish the child who can consent but who disagrees with the family rule from a child who cannot consent and disagrees with the family rule. In each case, the child dismisses parental authority. Superseding the child's wants is difficult, but may be more ethically defensible if he or she is not capable of consent. These situations, in which the child and parents disagree, frequently involve dissension, anger, and complications. Despite these complications, each scenario, at its core, has an assumption that the parents are behaving with the child's best interests at heart. In such cases, a member of the healthcare team may aid the family in identifying the objectives of the parents, child, and healthcare provider [16]. Through such discussion, a resolution may be reached.

Foreman describes a fifth case, in which unethical parents make what Foreman refers to as an "irrational" decision regarding their child's treatment, i.e., offering consent that ignores or recklessly disregards a child's benefit. Essentially, this circumstance disconfirms the child, rendering him or her nonexistent. Rather than using the family rule approach, the American Academy of Pediatrics recommends that "the cultural and family values, roles, and structure that have always governed the [child–parent] relationship should be treated with due respect" [4, p. e1445]. This statement is sufficiently vague so that its value in reducing child/parent conflict and promoting decision making is weakened. However, the position that the healthcare provider has an obligation to act in the child's best interest can be useful in situations in which there are cultural or role conflicts.

In their attempt to extend the Patient Self-Determination Act [17] to address involving adolescents in medical decision making, McCabe and colleagues (1996) frame their position based on the many situations in which adolescents have autonomous involvement in medical decisions [8]. They claim that, because in many states adolescents have autonomous involvement in medical decisions such as testing and treatment for sexually transmitted diseases and reproductive care, the views of adolescents should be solicited in other medical circumstances to protect his or her best interests. The authors propose that adolescents' capacity for decision making should be evaluated according to the legal requirements for informed consent and suggest that this assessment is most effective when performed by a healthcare provider who has an established relationship with the adolescent as well as with the parents. The latter suggestion, although important, is problematic in cases of fertility preservation decisions immediately following a cancer diagnosis; the healthcare providers are likely to be relative strangers to the family members.

When considering childhood cancer treatments, complications may emerge as decisions about cancer treatments and fertility treatments are addressed sequentially. Even in circumstances when cancer treatment decisions might be made openly and clearly by healthcare providers, parents, and (sometimes) a child, the addition of a treatment-related fertility threat may significantly alter the decision-making processes. Applying the family rule to the fertility preservation decision may elicit a joint agreement among the parents and the child, depicted in Foreman's first two conditions described above (child consents within the family rule and child either can or cannot provide fully informed consent so family moves to joint decision). Alternatively, one of the other three conditions will elicit interpersonal struggles as parents, children, and healthcare providers attempt to move forward. Family interaction practices, ranging from highly open to very closed communication, would impact the child's ability to provide consent within Foreman's ethical framework. In families characterized by closed communication, a child's consent may appear to be consenting within the family rule, but her lack of awareness of certain key information undermines that perception. In certain cases, this may reflect Foreman's fifth condition – parents offer consent that does not consider the child.

Other factors may contribute to limiting the decision-making capacity of family members or patients. An extension of Foreman's fifth circumstance (disregarding the child) may occur when healthcare providers provide neither parent nor child with information about the fertility threat inherent in the necessary cancer treatments – therefore, professionals ignore the family and the child's benefit. In their study of discussion of fertility issues before treating young cancer patients, Anderson and colleagues (2008) found that oncologists reported discussing the effect of treatment on fertility with 63% of patients, of whom 61% were viewed to be at high or medium risk of fertility problems [18]. Discussions were held more commonly with boys than girls, a finding that raises issues of gendered conversation practices that provide more information to males than females. In addition, the pressure for decision(s) comes at a time when parents may be both cognitively and emotionally overwhelmed, creating what is perceived as the major obstacle to informed consent related to pediatric cancer clinical trials [19] and, by extension, the fertility preservation decision.

## Family Communication and Ethical Decision Making: Issues and Complications

Having reviewed some of the general issues and complications involving medical consent when children face life-threatening cancer, a number of more specific factors related to family communication and decision making will be addressed. These include: (1) parental disagreement (2) complicated family forms, (3) assumptions inherent in biomedical language, (4) discussions at time of treatment, (5) discussions of sexuality, (6) discussions long after treatment, (7) keeping the topic a secret, (8) a child's rights to options, (9) parental/familial rights to options, and (10) decision based on current child vs. the forecasted adult child. All of these issues are compounded by the very short timeframe in which this decision must be made.

## *Parental Disagreement*

In two-parent legally constructed families, problems may arise if parents disagree, leaving the child aligned with one against the other. Child–parent disagreement remains a key area of concern, yet little is known about disagreements *between parents* when serious medical outcomes are at stake. The AAP's previously discussed stance on respecting the family structure can provide some guidance. Although the parents may disagree, if the "family rule" for a particular family is that one parent has decisional authority in most cases, it may be a way to resolve conflicts within the existing family structure. However, an adolescent should be respected for the "emerging adult" that he or she may become (p. 1447).

Few discussions of parental consent assume parental disagreement, although Foreman (1999) suggests that when caretakers disagree the healthcare provider has two responsibilities: (1) to do everything to bring the parents to agreement and (2) to recognize if agreement is impossible within the necessary time frame. The latter situation necessitates that healthcare providers must "support the child *against* the disagreement between the parents" (p. 494) and have the responsibility to side with the parent who appears to act in the child's best interest. Although this advice seems straightforward, criteria for this decision are not indicated. Many of these specialists are encountering a family for the first time, and many clinicians do not fully understand their options to provide the best care. Therefore, when it comes to fertility preservation, there is no clear indication of what would be in the child's best interest based on prior contact with the child or family. In their study of clinicians' knowledge of informed consent, Fisher-Jeffes et al. [20] described a fictitious scenario to healthcare professionals in which married parents disagree about chemotherapy for a 5-year-old leukemia patient. Only 65% of the pediatricians and 36% of other health practitioners knew that they could obtain consent solely from the mother who supported the treatment. The rules concerning consent may be even more complicated in situations in which the child is eligible for a clinical trial, as some protocols may require both parents to agree before entering [21]. Given that the majority of pediatric cancer patients receive some form of treatment through participation in a clinical trial [22], it is understandable that there is much confusion on the part of healthcare providers.

Beyond the immediate decision of what to do regarding the child's treatment, this issue gives rise to the following concerns: what are the long-term outcomes of the healthcare provider colluding with one parent against another on the adult marriage or partnership? On the parent–child relationship? On the future relationship with the healthcare provider? The professional's decision to follow one parent's decision against the other's, even if considered necessary, opens the possibility of irrevocably altering the marital and family dynamic, as this might become a relational turning point and an event referenced in any future disagreements.

## *Complicated Family Forms*

Surprisingly, the medical ethics consent literature seldom addresses the variety of family structures; rather, it tends to assume a two-parent biological family, only one of many minority family forms in the United States today. Contemporary families shatter any traditional understanding of "family," reflecting an "increasing diversity of self-conceptions as evidenced through structural and cultural variations, which challenges society to abandon traditional nucleocentric biases, cultural and traditional gender assumptions" [23, p. 5].

Currently, no majority family form exists in the United States. Even the two-parent biological family represents slightly less than half of US families. If one majority form were to emerge, it is likely to be the stepfamily. Stepfamilies, married and cohabiting, provide parenting for more than 4.4 million children [24]; these may include second and third stepparents from one parent's third or fourth marriages. More than a quarter of children live in single parent households, usually headed by mothers [25]. Currently, 2.5% of children younger than 18 are adopted [24], and, in a small but growing number of cases, children are raised in households headed by same-sex partners and foster parents. In lesbian-headed households, the children may be biologically related to one parent, and different children may have different biological mothers. For male or female same-sex couples, there may be legal barriers to both parents having legal authority over decision making, even in intact relationships [26].

One pressing issue involves understanding which family members play a significant role in making fertility preservation decisions or communicatively influencing healthcare decisions. This reality provokes several questions. For example, what happens when a biological father, who has played a very minor role in his daughter's life, attempts to override the decision of a former spouse and custodial stepfather, who together raised the 12-year-old child since age 2 and know her dreams for her future? What moral authority belongs to the man who raised the child as his daughter?

The variety of family forms raises questions with ethical implications such as: what right does the long-term cohabiting stepfather have to influence the decision making? Because of the tremendous increase in "open" adoptions, what rights might an involved birth mother play in the decision? A related sperm donor? Custodial grandparents? Further, where legal guidance exists, it is difficult for healthcare providers to know all the regulations.

## *A Child's Right to Options*

By and large, society thinks of an individual as having a right to reproduce, although this pro-natalist view is more pronounced in some societies than in others. In general, "[t]he right to procreate is inherently regarded as a moral 'negative right', which is to say that others have a duty to not interfere with this right unless there is sufficient and weighty moral ground to do so" [27, p. 167]. However, this position does not go as far as to say that others should "guarantee the right regardless of cost," making it a positive right. But by having decisions about fertility preservation in one's hands, parents may feel that not acting on options open to them is immoral. That is, for one's own children, fertility may be seen as a positive right that they have the burden of trying to preserve. Preliminary data from interviews with parents whose very young daughters have had cancer indicate that may be a concern [28]. Parents speak of wanting to "preserve" the child's opportunity for a "normal" life – not that she *must* have children but that they want all doors open to her – "just like anyone else." These parents are reluctant to allow a female child to lose options for motherhood. Parents may feel responsible for any secondary effects of the cancer treatment, such as infertility, because they approved the treatment that caused these effects. Some bioethicists speak of a child's "right to an open future" [29], i.e., that a parent should keep options open to children until they develop the maturity to decide for themselves. Although certain experiences can remove or add potential options for children, what obligation does a parent have to maintain a child's right to procreate?

## *Parental/Familial Rights to Options*

In addition to the child's rights to options, under what conditions might family members' preferences hold weight in decision making? John Hardwig (1990) argues for the rights of family members in medical decision making based on the assumption that a family is an interdependent relational system [30]. He asserts that, "The requirements of justice and the needs of other patients (meaning family system members) must temper the claims of autonomous patients" (p. 5). Hardwig believes that in the many cases, when important interests of family members are dramatically affected by the patient's treatment, "medical decisions often should be made with those interests in mind" (p. 5). He suggests that in certain situations, the interests of family members ought to override those of the patient, arguing that, "To be part of a family is to be morally required to make decisions on the basis of thinking about what is best for all concerned, not simply what is best for yourself." (p. 6) He states, "It could be argued that, in certain cases . . . it is irresponsible and wrong to exclude or fail to consider the interest of those who are close."

This position could raise questions related to interests of preserving the family line as well as interests of all children in the family. For example, what are the rights of parents who have only one child and wish to preserve the family line through biological grandchildren whose 13-year-old daughter refuses to undergo an experimental procedure to create an option for future parenthood? In a patriarchal culture, does the great-grandfather have the right to demand that a grandchild's fertility be maintained? Expense is not an insignificant factor. What is the parents' or family's responsibility to pay for fertility-related treatments, since it is likely to be very expensive and not covered by insurance? Could this expense put higher education or other goals out of reach for other children in the family? Does the family has an obligation to, for example, mortgage their home in order to pay for these treatments?

At what point do the expenses become the child's burden and responsibility? Davis points out that costs in the range of US $50,000 are not unheard of in the realm of "directed procreation" (such as pre-implantation genetic diagnosis) [31]. Davis argues that making certain investments (financial and otherwise) in children may result in parents feeling as if they have an entitlement to the choices the child makes in the future.

## *Difficulties and Assumptions Inherent in Language Used by Biomedicine*

Biomedical language is often constructed to fit the needs of the healthcare providers and the healthcare system. However, there may be biases inherent in such language. In this particular context, the language of cancer, its treatments, and its potential consequences on fertility are often unclear.

First, despite the scientific terminology, risks, benefits, and sequelae are often presented in non-specific terms related to the unknown future. That is, one cannot say with complete confidence how long one has to live, if a treatment will result in infertility, if a treatment will result in a response (even what a "treatment response" is may be somewhat subjective and the clinical connotation may not be clear to the parent), and so on. There is vast evidence that most people do not understand health risk information [32–38]. This information is often presented as percentages and probabilities filtered through the lens of the particular healthcare practitioner and his or her professional biases and experiences. How can informed decision be made if the implications are not clear to the decision makers?

Second, the terminology used promotes a normative expectation that holding to an ideal of a body and future unaffected by cancer is the desired standard. For example, fertility-related language includes terms such as "fertility preservation" and "loss of fertility," implying that a change in a biological function is seen as a change from the norm and as a loss that must be rescued. In addition, presenting even experimental fertility-related options to children and their families may imply that all children, and particularly all girls, will want to be biological parents. The idea that femininity is tied to biological motherhood and that one's role as a mother should be protected is not new. However, just as a child has acquired the label of "cancer patient," the introduction of fertility and other late effects of cancer move the child into the realm of "cancer survivor" and even, though she may be prepubescent, "infertile." The social, medical, and even insurance implications of this labeling are far from clear.

## *Discussions at Time of Treatment*

Given the stresses and time pressures emerging as families face a child's cancer diagnosis and then the fertility-related issues, reflective decision making is challenging. A request that parents consider enrolling their daughter in a clinical trial aimed at preserving fertility arrives at a time when parents may be in a state of shock. Another medical procedure of uncertain benefit may be more than they are willing to consider, especially if they perceive it would upset their daughter or there are other extenuating circumstances such as money or family tension [19].

What rights would the pre-teen or teenage daughter wish for in this situation? In a study of teen and young adult cancer survivors, the respondents strongly supported telling patients about the potential impact of the treatment on fertility at the time of diagnosis and indicated a desire to be treated as partners by their medical professionals, thus prioritizing their input over that of their parents [39]. In their analysis of healthcare providers' perceptions of children's decision making in healthcare, Runeson, Enskar, Elander, and Hermeren found timing and staff attitudes affected a child's role in the process [40]. In addition to showing respect for the adolescent, the AAP also suggests a model of decision making in which the physician or parent could play the role of "educator, discussant, challenger, and shared decision maker" [4, p. e1447]. In this way, disagreements between child and parent can be examined in a discussion that allows each party to think through his or her feelings, values, and concerns. Similarly, some advocate asking parents difficult questions in order to engage family members in a process of being truly informed and ensure that parents consider the best interests of the child as potentially separate from their own interests [41].

## *Discussions about Sexuality*

Communication about fertility is, by necessity, communication about sexuality. The ease with which parents may address the issue of future fertility will depend, in part, on the family history of open sexual communication. Research on parental communication about sex indicates that mothers are the primary communicators on sexual topics, although friends are the main source of sexual information. Fathers may discuss sociosexual issues with their adolescent daughters [42]. Some parents remain uncertain about how and when to initiate such conversations because they lacked good role models in their own lives [42]. Others report difficulty discussing sexuality because they doubt their own knowledge and skills, worry that their children will not take them seriously, or believe that raising the topic could be considered providing permission to engage in sexual activity [43]. Whereas sexually healthy families are characterized by effective and flexible communication patterns that support intimacy, sexually neglectful families exhibit an absence of discussion on the topic, and sexually abusive families reflect a perpetrator-victim pattern with limited communication [44]. Yet, Warren asserts that satisfaction with family discussion about sex is dependent on mutual dialogue [45]; this occurs when parents facilitate conversations and an attitude of openness prevails. By extension, discomfort discussing sexuality challenges parental perceptions of their own competence and willingness to discuss fertility.

Parental anxiety regarding discussing sex contributes to the following questions: Are parents who have avoided or downplayed discussions of sexuality prepared to hold such conversations about fertility and potential fertility loss under high-anxiety conditions? Are they obligated to find a medical professional or another known adult to represent them in such conversations? Communicating about a potential surgery or other fertility preservation procedure with no immediate benefit requires that parents view their children as sexual beings. Parents who are already uncomfortable discussing sex and sexuality are now confronted with the need for the discussion, perhaps even earlier than they would have thought necessary. They have to think about sex in a medical context (which could make the task easier or harder for them, depending on their views). This also requires considering how to "simultaneously retain and abandon the sense of the innocence of the child, while introducing the violation and risk of surgery and the consideration of the child's future sexual preferences, plans and reproductive life" [46, p. 23]. However, if it is unknown whether or not she is infertile, these discussions also highlight the need to discuss birth control to avoid unintended pregnancy.

## *Disclosing the Decision in the Future*

To what extent is there an ethical obligation to talk about the fertility-related decision as a very young child ages? When and how should she learn that her parents rejected or accepted the optional treatments or procedures? How is the choice to reject the option explained? How is the treatment discussed if a daughter does not remember undergoing a fertility preservation procedure? In certain cases, the initial explanation may need elaboration as childhood patients move toward adulthood. In other cases, parents may disclose that a daughter might have serious to minor difficulty achieving pregnancy.

For some young children, the issue is likely to emerge years later, often due to the need for hormone treatments or when infertility issues arise. If a family was not open in discussing sexuality, it will be more difficult to discuss the "unknown" or vaguely remembered procedure. Veiled comments may be expected to suffice when clarity and detail are needed. As evidence of such parent–child communication discomfort, Balen and Glaser report that medical practitioners find that taking medical histories may be complicated when dealing with treatments during childhood if the young person's parent is present [47]. They found adolescent patients were embarrassed about discussing topics such as menstruation and sexual intercourse and only did so when parents prompted it. Yet an adolescent who is alone with a healthcare provider, but is unaware of her potential fertility problems cannot give an accurate history and may not understand what the practitioner is discussing.

A child who needs to see an endocrinologist in order to enter puberty will likely have these discussions in a medicalized context. This may reduce the burden on the parents to discuss the technical details of sexuality and fertility, but it does not negate the need to address the emotional components of this revelation nor allow the parents to rely on the adolescent to have a complete understanding of her situation. As she matures both emotionally and cognitively, these conversations are likely to reoccur.

In their study of teenagers and young adults faced with possible or actual fertility impairment following cancer treatment, Crawshaw and Sloper interviewed 38 cancer survivors (ages 16–30) [39], who were aware that their fertility might have been affected. Many did not learn about the fertility concerns until sometime after treatment. Some respondents found it difficult to talk openly with any family members about fertility issues. Families were much less likely to talk about cancer-related fertility issues than cancer issues at any time after treatment.

## *Keeping the Topic a Secret*

Secrets, such as a choice to pass on a fertility-related procedure or an undisclosed fertility-related procedure, leak over time. Attempts to conceal decisions related to a young daughter's future fertility limit family communication in unforeseen ways. It may transform, and potentially undermine, the child–parent relationship in later years. This becomes a toxic secret, a secret that impacts healthy relationships, disorients family identity, and limits member's abilities to make clear choices [48], eventually eroding trust in the parent–child relationship. If and when the secret is discovered through indirect means (e.g., a relative's comment or medical record access), the complications are multiplied. Finally, if and when a former patient, who was old enough at time of treatment to understand the implications, learns that the fertility threat was consciously withheld from her before cancer treatments began, painful family conflicts may follow.

Recognizing the costs of secrecy does not result in a clear and easy path. Revisiting a pediatric cancer experience is difficult for many families; some address the experience in very different ways for years to come. Long range research on parents and pediatric cancer survivors indicates that many parents experienced a higher level of concern about their child's health status and experienced more recurring thoughts about the child's cancer than did the patient [49]. Such ongoing cancer-related anxiety, coupled with a fertility-related toxic secret, would serve to alter the parent–child relationship in the years following treatment. Just as family members who do not wish to address a genetic disorder openly engage in scanning relatives' behavior in an attempt to see any signs of the disease [50], families that maintain such secrecy are likely to scan for signs of fertility-affected outcomes (e.g., absence of menstruation onset, long period of attempts to achieve pregnancy) as predictors of problems. If signs appear, more direct communication may follow. If a cancer survivor discovers, as an adolescent or young adult, that self-identity dreams, perhaps as a future biological mother, are not likely or possible, the relational "destruction" may be as serious as the news itself.

### *Decision Making Based on Current Child, Not Forecasted Adult Child*

A final set of concerns deals with the uncertain nature of the cancer treatments and their consequences. Parents are making decisions based on who a child is at the time of diagnosis, but, even if the child survives, she may have serious physical or cognitive problems depending on the type of treatments necessary. If the child becomes cognitively impaired, what happens to the stored tissue, eggs, or embryos? Who decides if the child, upon reaching adulthood, can or should have access to the stored tissue and any procedures necessary to turn the tissue or embryos to infancy? The parents do not yet know what disabilities their child may have, nor do they have experience in caring for a disabled child. Certainly, there are many people with cognitive or intellectual difficulties who become parents, but what rights do they have or maintain when considering parenthood using assisted reproduction, as would be necessary if using stored tissue?

## Conclusion

Female cancer survivors have reported that facing infertility can be as difficult as dealing with the cancer and related treatments [51]. This chapter has identified both a family-centered framework through which to examine fertility preservation for girls and their parents as well as presented a number of issues and complications related to ethics and communication in the pediatric cancer context. There are three important omissions in much of the bioethics literature regarding families and participation in decision making. First, there is no majority family form in the United States, yet much of the bioethics literature assumes two biological parents will be involved in decision making. Second, the literature also seems to assume that if there are conflicts or difficulties, these will be between the child and (two) parents – not that parents might disagree with one another. Third, little attention is given to the role of others, such as a grandparent who may serve as the family matriarch or patriarch and a healthcare decision maker. Furthermore, the decisions made have long-lasting repercussions on the child, some of which she may not be aware at the time of treatment. How to discuss sexuality and fertility, when to discuss and revisit the discussions, and how to ensure that the child both understands and develops her comprehension as she grows are all topics that must be contemplated and addressed. Healthcare professionals and family members face multiple ethical and personal challenges when a daughter faces potentially fertility-threatening cancer treatments – yet these challenges reflect the significant medical advances that are developing fertility preservation options. Skilled healthcare providers (perhaps including counselors and social workers) may be able to ensure that all voices are heard and that ethically responsible decisions are being made with children and families. Hopefully, the communication involving professionals and family members will lead to family-specific resolutions consonant with their beliefs and values.

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# Chapter 34
# Choosing Life When Facing Death: Understanding Fertility Preservation Decision-Making for Cancer Patients

**Shauna L. Gardino and Linda L. Emanuel**

## Framing the Paradox: Understanding Reproduction in Current Society

On a fundamental biological level, humans are programmed to reproduce; hormonal and physiological influences are reinforced by social pressures and structures that urge parenthood in most cultures. The inability to reproduce usually causes distress and suffering among men and women alike. The advent of assisted reproductive technologies such as embryo/egg banking and in vitro fertilization has changed the face of reproduction, offering the possibility of parenting to a wider range of individuals who formerly were unable to reproduce. Although these controversial technologies have arguably blurred the boundaries of what it means to be a family or to parent a child, their wide use reveals that reproduction, particularly biological reproduction, holds great value. People find parenting their own genetic child compelling. Apparently a deep desire to propagate our own germ line is part of who we, as people, are.

The emergent discipline of oncofertility, an intersection between oncology and fertility, recognizes that cancer patients and cancer survivors have legitimate concerns about their fertility. Common cancer treatments such as chemotherapy and radiation pose a great threat to reproductive functioning, and infertility is an all too common side effect of cancer therapy. Oncofertility addresses these concerns, using both existing fertility preservation technologies and developing new techniques to accommodate the unique concerns of cancer patients. These new technologies place the patient in a somewhat precipitous position, paradoxically thinking about procreation at a time when one's own life is at stake.

Elements of this paradox, however, are not new. Rather, technology has engendered a new instantiation of this ancient intersection of procreation and death. Maternal mortality was a historical threat facing pregnant women, yet did not deter the majority of women from attempting childbirth. Although maternal mortality has

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largely been eradicated in the Western hemisphere, childbirth remains a prominent risk for women in the global South. Each year across the globe there are more than half a million pregnancy-related deaths, with most women readily assuming the risks associated with childbirth [1]. Likewise, fathers have demonstrated their drive to reproduce in the face of an uncertain future, often leaving their wives with child when they embark for war. World War II provides a case in point: in the 1930s the birthrate in the United States hovered between 18.4 and 19.2 live births per 1,000; it increased to 22.7 in 1943, the height of the wartime baby boom [2, 3]. Today, it is becoming more and more common for soldiers, both male and female, to bank gametes before leaving for war, a modern twist on the old practice of siring before leaving for war [4]. Certain fertility preservation facilities even offer discounted rates for soldiers and the nation's "first responders" – firemen, policemen, paramedics, and emergency medical technicians – wishing to preserve their sperm [5]. This drive to procreate in the face of adverse circumstances has manifested itself in human populations across both temporal and geographical boundaries and continues to impact reproductive choices.

Modern reproductive technologies are presenting cancer patients, practitioners, and society with a new version of this universal dilemma: how to procreate successfully when faced with death. This crisis is shared between the human, animal, and plant kingdoms, as evidenced by particular animal and plant species. In the animal kingdom, male octopuses die within a few months of mating and female squid often die right after their offspring hatch. More dramatically, the female praying mantis eats the male praying mantis to initiate copulation, and the female black widow spider eats the male black widow spider post copulation. In the plant kingdom, annual plants such as corn, lettuce, pea, and marigold usually die within 1 year of germination. The hemp plant dies soon after it flowers. Certain species within the plant and animal kingdoms demonstrate a similar reproductive resilience as seen in humans, opting to pursue procreation when facing an uncertain future.

While the fundamental issues at stake have historical roots, the personal accounts, experiences, and patient cases represent novel facets of familiar themes. Oncofertility emerged from the unmet, compelling desire for fertility preservation options as expressed by cancer survivors themselves. This commentary explores fertility preservation for cancer patients, analyzing the unique intersection of life and death that these individuals face and reflecting upon the potential mechanisms that drive these profound reproductive decisions. It begins with a discussion of fertility preservation for women facing a cancer diagnosis, commenting on motherhood and maternal instinct and how these concepts are understood both in society at large and among cancer patients. An assessment of fatherhood in the face of cancer follows, including a discussion about the role of the father in current society and how the responsibility of fatherhood is managed by male cancer patients. Fertility preservation for pediatric cancer patients is examined next, highlighting the specific concerns and considerations for this vulnerable population. The latter portion of this chapter is devoted to understanding *how* cancer patients manage the inherent life/death confrontation in making fertility preservation choices, *what* coping mechanisms may come into play in this process, and *who* can help these patients navigate these complex decisions in the clinical setting.

## Motherhood in the Face of Cancer

Women facing a cancer diagnosis have fewer and less successful options to preserve their fertility compared to males, placing them in a precarious position regarding their ability to procreate in the face of cancer. While some female cancer patients may be able to delay cancer treatment to pursue embryo or egg banking, more severe cancer diagnoses as well as other circumstances (such as a lack of partner or sperm donor) may prohibit women from taking advantage of these more successful techniques. Pre-pubertal females are not eligible for embryo or egg banking. For the women still desiring biological motherhood, investigational techniques such as ovarian tissue cryopreservation provide hope for a future pregnancy, but, as of yet, fewer guarantees of success. The popularity of oncofertility clinical trials demonstrates that not only are women interested in these investigational techniques (even though they know the methods may never reach fruition) but they are also actively pursuing them[1] (Gerrity, September 3, 2009, Personal conversation). What factors drive these decisions and how is the crisis of facing death mitigated by the desire to produce life?

Fertility preservation efforts must be undertaken before the initiation of cancer treatment, at a time when a woman's body is disease-laden. A woman pursuing fertility preservation is thus seeking to secure her physical capability to produce a new life during a time when her body cannot necessarily sustain its own life. The juxtaposition of life and death and of health and disease is an extraordinary example of the core instinct to mother. In the face of famine, warfare, and devastating diseases such as HIV/AIDS, females have shown that the instinct to give birth and create life is sustained [6]. But why? And how? Does one's fear for one's own survival sometimes outweigh the desire to create a future life?

To explore these questions we started with this one: what is driving these maternal desires? Some argue that this "maternal instinct" is something women are born with; others contend that society grooms women to become mothers. Both interpretations hold merit, and each can offer insight into the mechanisms that play out during fertility preservation decision-making for cancer patients. This section will explore and outline each interpretation, emphasizing the relevance of these concepts in the context of fertility preservation decision-making and describing how they almost certainly work together in this instance.

The desire to become a mother is often presented as an innate characteristic, a mammalian manifestation of hormones and impulses that urges women to reproduce. As S. Philip Morgan and Rosalind King describe, humans have genetically determined forms, sensitivities, and physical and emotional reactions that encourage sexual activity; these are underlying genetic predispositions that have sustained our species throughout time [7]. While the biological underpinnings of

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[1] Of the approximately 300 women who requested fertility preservation consultations at Northwestern University in the past year and a half, approximately 75 chose to pursue a fertility preservation intervention, including embryo banking (*n*=53), oocyte banking (15), and ovarian tissue cryopreservation (*n*=7) (Gerrity, September 3, 2009, Personal conversation).

this desire are debatable (a desire for sex could easily be misinterpreted as or confused with a desire for motherhood), it is indisputable that complex and shifting physical, psychological, and emotional changes develop in maternal physiology during pregnancy [8]. Without this biological programming, humans would probably have perished many eras ago. This underlying genetic drive that shapes the pregnancy experience and parenting strategies thereafter is shared among the human and animal kingdoms. Mothering (and parenting) strategies are remarkably consistent across a diverse array of species, including monkeys, mice, seals, birds, and spiders, suggesting a highly conserved set of genes that drive them and pointing to potential underlying physical similarities in the birth process and development of parenting habits [9].

In humans, intense hormonal changes characterize pregnancy, with human chorionic gonadotropin hormone (hCG), human placental lactogen (HPL), estrogen, and progesterone playing major roles. Changing hormone levels can contribute to a variety of changing emotions. While pre- and postnatal hormonal changes are involved in the rapid onset of mammalian maternal behavior at birth, there is no known formula or combination of these hormones that ensures the "mothering" instinct in women [10]. Individual women respond differently to each pregnancy and birth experience. While there are biological influences apparent in pregnancy desires and behaviors, these forces do not act alone; social forces, pressures, and structures often reinforce both maternal desires and parenting behaviors.

Our current social structure is indeed rooted in a defined role of "mothering," a sexual division of labor in which women parent and men are active in the labor force. Sociologist and psychoanalyst Nancy J. Chodorow argues that people talk about a man "mothering" a child but are not likely to talk about a woman "fathering" a child; if this is the case, being a mother is not limited to giving birth, and the roles of "mother" and "father," although grounded in biology, are also social [11]. While fathering is primarily defined as a siring role, mothering entails a lifelong caregiving role, and motherhood is not limited to the singular event of childbirth. Biological impulses may urge women to have children, but society guides them in developing parenting habits and designating family structure.

As medical ethicist Janice G. Raymond describes, motherhood is fundamentally relational [12]. Although a biological capacity, motherhood occurs within a social, political, and historical context. If motherhood is shaped by sociocultural factors, then the desire to partake in this greater social role must originate at least in part from society. Perhaps, as postulated by psychologist Daphne de Marneffe, the maternal desire may not be created by a social role but is indeed supported by one, namely the gender role of women [13]. If this is the case, then the plausible biological and hormonal impulses to mother are sustained and supported by society. In this way, a combination of biological and social factors may lead women to deeply desire their own biological children and guide them in nurturing and "mothering" their offspring. But what drives women to desire and accept this role of a mother?

de Marneffe argues that the desire to mother is not only the desire to have children, but also the desire to care for them, and that maternal desire is, "the longing felt by a mother to nurture her children; the wish to participate in their mutual relationship; and the choice, insofar as it is possible, to put her desire into practice" [13]. But from where does this "longing" originate? Raymond contends motherhood has been constructed as an instinct, a biological bond with a child, or an unquestioned state of being that is the essence or pinnacle of female existence [12]. It is reasonable to assume that each of these features describes a part of what drives and constitutes motherhood. Therefore, we assume that a combination of biological, physiological, and social factors interact to influence reproductive choices.

Given the importance of motherhood to many women, it is easy to imagine a cancer patient taking preventative steps to ensure that she has an option to become a biological mother. The various forces (both biological and social) driving this desire or impetus to mother are crucial in understanding how to counsel and advise female cancer patients who are contemplating fertility preservation. The more complicated question of how an individual woman manages this decision to prepare for a future life when her own existence is in jeopardy will be assessed in more depth after exploring fertility preservation among both male and pediatric cancer patients.

## Fatherhood in the Face of Disease

Pubertal and post-pubertal male cancer patients facing a cancer diagnosis have a comparatively easy and effective option to preserve their fertility: they can bank a sperm sample and leave it frozen for decades until they are ready to become a father. The technology for freezing and thawing sperm is well established, successful, and relatively inexpensive. Men choosing to bank their sperm are responding to a counterpart reproductive impetus as seen in women. While the parenting desire in males shares commonalities with that in females, this drive is based on indistinct, sex-specific biological influences and gender-specific social influences.

Conventional wisdom claims that men have a stronger sex drive than women, with biological processes, particularly the substantial gender difference in testosterone, implicated in determining sex drive differences between men and women [14, 15]. This view of the male sex drive has historical roots but is also supported by quantitative biological evidence. Charles Darwin remarked that "males, with their superior strength, pugnacity, armaments, unwieldy passion and love songs, are almost always the more active and most often, the initiators of sexual intercourse" [16]. On a genetic level, demographer Lawrence C. Shimmin, along with colleagues, found supporting evidence that the evolution of DNA sequences in higher primates is male driven [17]. Biologists Rama S. Singh and Rob J. Kulathinal echoed this finding, evidencing how genes that possess sex-specific effects on male fitness accumulate to a much greater extent [18]. These specific genetic predispositions in the male may play a role in influencing men to desire biological children. Male biological and hormonal impulses to procreate may be driven by these underlying evolutionary mechanisms – safeguards that ensure propagation of the male gene and maintain men's interest in procreation.

How do biological and genetic influences translate into parenting behavior in men? Craig Rypma argues that similarities in parental behavior observed across cultures are indicative of biological (e.g., hormonal) influences, while perceived cultural differences in fathering can be viewed as learned responses resulting from social adaptations [19]. In an analysis of expectant fathers, psychologist Anne E. Storey found that men had similar stage-specific differences in hormone levels as women, including higher concentrations of prolactin and cortisol in the period just before the births and lower postnatal concentrations of sex steroids (testosterone or estradiol). Although these data do not offer functional proof of hormonal involvement in paternal behavior, they nevertheless suggest that men exposed to appropriate stimuli undergo hormonal changes around the birth of their child that may facilitate the expression of paternal behavior [9]. Storey concludes that the apparent testosterone decrease in men during the postnatal period may enhance paternal responsiveness by reducing men's tendencies to engage in non-nurturing behaviors [9]. In sum, men's desire to reproduce may be accounted for by biological and hormonal impulses, evolutionary-driven genetic expressions that ensure survival for and propagation of the male gene. These biological and hormonal factors probably contribute to a man's decision to preserve his fertility even when faced with cancer. However, they cannot fully explain this behavior. Sociocultural influences must be explored as well.

As Lawrence M. Berger and colleagues argue, a purely biological-based conception of fathering is likely to have limited utility for fully explicating the parenting practices of both biological and social fathers[2] [20]. Indeed, socioeconomic, relationship, and personality factors combine and interact to influence fathers' involvement in child care [14]. In this way, the role of the father is not limited to his biological contributions, but extends to his relational roles in providing care for both the child and his family as a whole. A man's expectations of his role as a father, then, can arguably originate from social expectations and norms of fathering in general. The context in which men care for their infants and the meanings they create from their fathering experiences are frequently influenced by societal expectations [21].

The success of the available fertility preservation technologies is higher and the risks are lower for men when compared to women. As with women, biological and social influences compel men to become biological parents. Although the science of oncofertility is focused on mitigating the gender gap in terms of successful fertility preservation technologies, this should not justify overlooking male needs. Men have independently demonstrated that they too value their potential to procreate when faced with a cancer diagnosis, exhibiting a similar drive to reproduce as women [22]. The factors driving men to protect their ability to father are both biological and social. Recognizing these influences is crucial to helping men navigate fertility preservation decision-making in the clinical environment.

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[2] Social parent, as used here, refers to a parent who is responsible for everyday caretaking of a child but is not necessarily biologically related to the child [20].

## A Transgenerational Perspective

While the parenting instincts of men and women are relatively clear, the desire to parent among pediatric and adolescent cancer patients is a more complicated issue. Childhood cancer survivorship is on the rise, and these young cancer patients can now anticipate a life after disease. As this growing population begins to age, they will be faced with the consequences of cancer treatment, including potential infertility. Though scarce, some fertility preservation options are currently available for this cohort. Ejaculation can be stimulated in young boys and the resulting sperm cryopreserved[3] [23]. Pre-pubertal boys have fewer options; testicular tissue biopsy can be used to gather immature and developing sperm, but this technique is still investigational and offers no guarantees or assurances that a young boy will be able to father a child in the future[4] [24]. Pre-pubertal girls have only one option, ovarian tissue cryopreservation, which is also considered an investigational technique with no guarantees for a future baby.

Fertility preservation choices are particularly complicated for the pediatric and adolescent patients for a number of reasons. First, the young child may not be intellectually, emotionally, or psychologically developed enough to comprehend the situation and understand the implications of their decisions. Since children develop at different rates, no age-specific guidelines exist on when it is appropriate for young patients to make their own autonomous reproductive health decisions. For this reason, parental influence may drive decisions for the pediatric patient, with child assent and parental consent complicating decision-making. Second, both parents and physicians may have trouble viewing a young child as a future sexually mature being and thus find it difficult to make reproductive decisions on behalf of the child. Finally, as children mature, they may feel altered pressures to procreate because their parents invested time, money, and effort to preserve their fertility many years prior. For these and other reasons, parents and physicians alike play a key role in influencing the reproductive future of pediatric and adolescent cancer patients.

In deciding to pursue fertility preservation for their child, parents must act quickly, as fertility preservation efforts have to take place before cancer treatment can begin. Justifying this potential delay in treatment is a heavy task, as it may not always be clear what is in the best interests of the child. The nascent autonomy of the child may be compromised as parental and provider wishes for a child's future fertility may overshadow the expressed choices of the child. Parents and healthcare providers will often need to make heavy choices on behalf of young cancer patients, choices that will change the child's reproductive and sexual future.

Parents and providers may respond to fertility preservation choices for young cancer patients based on their own experiences with mothering and/or fathering, as

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[3] Two techniques can be used to stimulate ejaculation in young boys: penile vibratory stimulation, which is noninvasive and simple, or electro-ejaculation, which is more complicated and requires general anesthesia [23].

[4] Although this option requires invasive procedures, parents of boys surviving childhood cancer have indicate that this option is both desired and accepted [24].

well as perceived social stigmas that they fear the young patient may face once of reproductive age. Young patients who advocate for autonomy to make their own decisions may be responding to social influences, hints of biological urges, and perceived future desires to parent. Depending on the age of the young cancer patient, psychosocial reasoning may also come into play during the decision-making process. Understanding the forces driving these decisions is necessary for proper advising of young patients, if they are to be suitably voiced, represented, and advocated for.

The majority of pediatric and adolescent cancer patients will survive their disease, resuming their lives post-cancer with few lingering complications. Oncofertility technologies are intended to allow these young patients the option to become a biological parent should they wish. Fertility preservation for pediatric and adolescent cancer patients, however, is not a straightforward decision, as it often requires a delay in treatment and may not result in the potential to parent. Relevant concerns about surgical complications, treatment delays, future side effects, and false hope need to be addressed as they are raised by parents and young patients alike.[5] Clinical support teams composed of doctors, social workers, psychologists, and ethicists need to be available to help the patient, parent, and provider triad navigate these decisions.

## Decision-Making: Confronting Life and Death Simultaneously

Male, female, and pediatric cancer patients affirm the value of their fertility when choosing fertility preservation in the face of a cancer diagnosis, reflecting individual and social desires, expectations and influences. Although it is clear that cancer patients desire options and opportunities to preserve their fertility, the decision-making process at the point of cancer diagnosis remains unclear. How is the balance between life and death mediated and when does this balance become upset? When does the value of one's own life outweigh the value of a future, imagined child? It is difficult to answer these questions, but we can speculate that psychosocial coping mechanisms may come into play during the decision-making process, buttressing the biological and social impetus to preserve one's fertility.

Gynecologists Sibil Tschudin and Johannes Bitzer argue that cancer, as a life-threatening diagnosis, may evoke fear of death and coinciding feelings of suffering, pain, dependence, and loss [25]. Fertility, on the other hand, is associated with new life, hope, joy, pride, strength, optimism, sense in life, and growth. The hope associated with fertility preservation thus represents the opposite of a cancer diagnosis. Perhaps the positive emotions associated with fertility preservation overshadow the

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[5] As used in this chapter, "false hope" describes the circumstance when (a) expectations and response strategies are based on illusions rather than reality, (b) inappropriate goals are pursued, and (c) poor methods or strategies are used to achieve desired goals [31]. False hope becomes a concern for young cancer patients who undergo ovarian tissue cryopreservation or testicular tissue biopsy as these techniques are both currently in development and may never be successful.

negativity brought about by a cancer diagnosis; in the face of despair, people turn to a possibility of hope and cling to an imagined future to confront their dire present. Further, an imagined future of infertility can be as crushing as a cancer diagnosis. Both men and women have the capacity for relentless self-blame, guilt, and shame when it comes to losing something as instinctive and personally and socially important as the ability to have children [26]. Infertility often compromises self-esteem, identity, sexuality, and self-image [25]. Cancer patients may be eager to protect themselves against future emotional grief by preserving their reproductive options. Fertility preservation may be a preventative effort, an assertion that the future can offer a return to a normal life post-cancer.

Current cancer patients may also conceptualize parenting as a beneficial endeavor. de Marneffe argues that parenting is a creative act like no other, one of life's greatest pleasures for women; the act of motherhood enlivens a woman and allows her to discover parts of herself that simply would not exist were it not for her relationship with her growing child [13]. Psychologist Garret D. Evans and child and family development expert Kate Fogarty describe the benefits of being a father to include the enjoyment of secure relationships, enhanced coping skills, larger support networks, more pride in one's job, and greater self-confidence [27]. In this way, cancer patients are not only preventing future distress but are, in a way, trying to ensure future happiness.

But the future fertility of the currently ill patient is by no means guaranteed. Ovarian cryopreservation is still an experimental technique, and even women who opt for embryo or egg banking are not promised a healthy pregnancy and baby. These developing technologies leave room for heightened expectations and, ultimately, false hope. In an effort to protect their future happiness, cancer patients may actually be setting themselves up for future emotional distress. These individuals may be presuming a parenting role that they eventually will not be granted.

Bioethicists John D. Arras and Jeffrey Blustein argue that it is irresponsible to have a child if you cannot meet child-rearing responsibilities, and psychologist Lisa Cassidy claims that people who anticipate not being excellent parents should not parent at all [28, 29]. But we assert that fertility preservation patients are not irresponsible when electing fertility preservation. They are not making the decision to have a child, but rather protecting their potential to parent. Judgments pertaining to an individual's parenting decisions must be withheld until the individual has taken the steps necessary to actually become a parent. Since fertility preservation for cancer patients is an emerging field, few pregnancies have actually been attempted using the experimental techniques developed specifically for cancer patients (such as ovarian tissue cryopreservation).[6] In our experience with patients from our own programs, patients demonstrated considerable thought about both the actions of attempting to preserve their fertility and the choice of when (if ever) to parent. As

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[6] Many successful pregnancies have resulted from well-developed fertility preservation techniques such as sperm banking and IVF, among both the general population and cancer survivors as well. Fewer pregnancies have been attempted using ovarian tissue cryopreservation as the technique is still considered experimental.

patients are not choosing to attempt pregnancy at the time of cancer diagnosis (or even shortly thereafter), they are attributing a value to their future, imagined self, an individual who may be more fit to parent.

Cancer patients who choose to preserve their fertility are making a statement that they value their reproductive capacity and options. In the face of a potentially fatal cancer diagnosis they show optimism for the future and assert their potential to parent. Options are preferred over no options, even if outcomes remain uncertain. Fertility preservation choices may be a coping strategy for patients facing a cancer diagnosis, providing hope for a return to a normal life post-cancer.

Psychologists Stephanie Jean Sohl and Anne Moyer define proactive coping as a method of assessing future goals and setting the stage to achieve them successfully, a process through which one prepares for potential future stressors, possibly averting them altogether [30]. Aspiring to a positive future has been found to be distinctively predictive of wellbeing. In the moment of decision-making, biological impulse combines with social pressures and psychological reasoning to influence patient's choices. The intersection of these forces is likely complex, but recognizing that psychological factors are at play as well can help to inform practitioners and patients as to how to make the best choice for each individual.

## Implications and Conclusions

Male, female, and adolescent and pediatric cancer patients who choose to pursue fertility preservation in the face of a cancer diagnosis demonstrate faith and attribute value to their capacity to reproduce at a time when their physical bodies are at risk of not supporting their own lives. Modern science is offering a new option to cancer patients, an option that forces patients to think about creating a new life at a time when their own life is being questioned. New oncofertility technologies follow a greater scientific and medical trend that is challenging definitions of parenting, dissociating parenting from historical limitations, and offering the potential to parent where there previously was none. As such, new conceptualizations of parenting will surface as cancer survivors begin to parent post-cancer. Patients, practitioners, and society alike need to be aware of these new paths to parenthood and understand that they are new manifestations of an old theme: the desire to be a parent. Understanding the biological, social, and psychosocial roots of these parenting desires can hopefully help healthcare practitioners in best counseling their patients during the decision-making period and thereafter.

The novelty and immaturity of oncofertility technologies reflect the uncertainties of these techniques in clinical practice. Should these technologies prove unsuccessful for the majority of cancer survivors, the medical community will shoulder the blame. Oncofertility in clinical practice necessitates a team of interdisciplinary scholars, including scientists, physicians, social workers, psychologists, ethicists, and so on to come together and share their expertise in how to best counsel cancer patients interested in fertility preservation. Fertility preservation for cancer patients presents a new face to a familiar theme, affirming the universal desire to parent among a previously unacknowledged population. These expanding technologies have the potential to change the trajectory of cancer survivorship. Reflective and critical scholarship must accompany scientific and medical advances in a continuous and focused effort, examining how cancer patients process this complicated decision and how cancer survivors react to their choices years down the line.

Oncofertility technology allows humans to further distance reproductive options from biological constraints, raising fears about regulation and ownership of reproductive materials. The long-term storage of genetic material complicates decision-making for cancer patients, since ownership of the material in the event of death needs to be decided before the patient undergoes fertility preservation. Fertility preservation choices should be made in a supportive and informative environment, with legal experts present to help patients understand their rights and establish ownership stipulations for reproductive materials in case of adverse events. Advance planning is necessary to prevent future complications. Although wishes may change over time, individuals remain legally bound to their original choices. Patients (or their partners) who change their minds need to be counseled on their decisions and provided with coping strategies to come to terms with their choices.

Male and female cancer patients, both adult and pediatric, should not have to make fertility preservation decisions alone. Rather, they should have access to guidance, support, and trained professionals to help them navigate this intersection of life and death. Fertility preservation decision-making for cancer patients is not a single event but rather a larger journey, an emotional experience that is influenced by biological, social, and psychosocial forces interacting with modern medicine. Healthcare providers must be aware of the underlying mechanisms guiding these decisions in order to provide the best care for their patients both at the time of cancer diagnosis and years later, when parenting desires may resurface.

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# Part VII
# Healthcare Provider Stories and Final Thoughts

# Chapter 35
# Discussing Fertility Preservation with Breast Cancer Patients

**Jacqueline S. Jeruss**

## Introduction

Approximately 180,000 women are diagnosed with breast cancer each year. Of these patients, over 16,000 are younger than age 45 [1]. Receiving a diagnosis of breast cancer is difficult regardless of the patient's age. Simultaneously, the impact of this diagnosis for younger premenopausal patients may be particularly traumatic as the implications of the diagnosis may have an added morbidity of fertility loss. Navigating the issue of fertility in the midst of a new cancer diagnosis is complex for both the patient and the physician. This complexity primarily stems from the relatively short time frame available to organize a plan of care that encompasses all the patient's needs, both oncologically and for fertility preservation. The emergence of the field of oncofertility has enabled a more streamlined approach to the newly diagnosed breast cancer patient who has a desire for fertility preservation. Through the interdisciplinary effort of reproductive specialists in cooperation with oncologists, young breast cancer patients are now meeting the goals of cancer treatment with a greater hope for preserved fertility during survivorship.

There are several different objectives to be met during the initial consultation for a new breast cancer patient interested in fertility preservation. At the outset, the patient's general level of anxiety must be assessed and reassurance provided. For patients with a great deal of diagnosis-related anxiety, the ability to process and retain new information can be very difficult. Accordingly, the amount of new information conveyed to the patient must take place in a stepwise fashion that suits the patient's capacity to participate in this important conversation. Typically, at the time of presentation, the patient has already undergone several radiographic and interventional diagnostic tests. Often, a discussion of these tests and their findings is reviewed at the outset of the consultation. This helps to ensure that the patient and the physician share an understanding of the diagnosis and any additional tests that

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may be necessary to establish a cancer treatment plan. The patient's medical history is then reviewed in detail. This history includes the patient's prior illnesses or hospitalizations, medications, family history of cancer, and a precise history of hormone exposures including birth control pills, fertility treatments, and supplemental estrogen therapy. Additional information is obtained about the onset of menarche, as well as the patient's childbearing and lactation history. It is during this time that the subject of fertility preservation may be initially discussed. Often a simple question, such as "Were you thinking about having a child?" or "Were you planning to have any more children?" can help get the patient to begin thinking about her fertility. The patient is then examined and the conversation typically refocuses to the plan for cancer treatment. Once the initial cancer treatment plan is outlined, which often includes a combination of surgery, chemotherapy, and radiation, the issue of fertility preservation is then readdressed. By this point in the visit, the physician may either know or can reasonably speculate on the likelihood that the patient will require chemotherapy as part of her care. The inclusion of chemotherapy in the treatment plan poses the greatest fertility risk for breast cancer patients. Once the patient is informed of the potential need for chemotherapy, she may then be more focused on the immediate threat to her fertility, unlike the patient who will not require this component of breast cancer management.

When a patient with a fertility threat is interested in options for preservation, often a detailed discussion of the potential options for fertility preservation is held at the end of the initial breast cancer consultation. The level of detail in which these options are discussed is entirely dependent upon the patient's ability and desire to obtain more complex information while establishing a cancer treatment plan. While it is at times difficult to address an additional critical subject after discussing the cancer treatment plan, the sooner the patient's fertility issues are addressed, the greater the chance that the fertility preservation measures will occur without any need for delaying cancer therapy. Subsequent to completion of the initial visit with the oncologist, if possible, the patient should undergo counseling about fertility preservation during a separate encounter with a fertility preservation specialist. If the patient desires this meeting and it can be arranged, the second consultation may occur on the same day as the initial cancer consultation. If the patient has a partner who was not present for the initial cancer consultation, often the fertility preservation consultation will be deferred to include both the patient and her partner.

The significance of a second consultation with a fertility specialist is several-fold. Although the oncologist may have the best intentions regarding meeting all of the patient's needs, it is difficult to discern if some bias against fertility preservation measures, in favor of a more simplistic and traditional cancer care plan, may affect the ability of the oncologist to present a balanced approach to fertility preservation options. Simultaneously, the patient may associate the oncologist primarily with cancer management and may not be able to think beyond cancer care to issues of survivorship while in the presence of an oncologist. Meeting separately with the fertility preservation specialist who will be providing the care necessary for fertility preservation allows patients to think about the future and survivorship without simultaneously being faced with the present and the impact of the new cancer diagnosis. While some patients may be ready to meet with the fertility specialist immediately after the cancer consultation, it may be optimal for most patients to have this second consultation a few days after the initial cancer plan is established to allow for time to process new information and to prepare for additional decision making. The appropriate coordination and timeline of these visits should be determined by the patient and the oncologist on an individual basis.

Some young cancer patients will require chemotherapy before surgery due to their more advanced stage at presentation. For these patients, fertility preservation options will take immediate precedence in the patient's overall management plan and will need to be rapidly facilitated. Most patients undergo surgery as the initial step in their cancer care. For some of these patients, the need for chemotherapy will only be determined after definitive pathologic information is available. Additionally, for those patients whose tumors will undergo advanced genetic assessment to help establish the need for chemotherapy, the time between surgical recovery and the start of chemotherapy can be up to 1 month. This time interval should allow sufficient time for several fertility preservation interventions without disrupting the flow of the cancer treatment plan. It is critical to utilize the window of time prior to the initiation of chemotherapy, not only because this treatment may last from 4 to 6 months and permanently damage fertility but also for some patients, additional treatment may be necessary that may delay potential fertility interventions for up to 1 year. Furthermore, for approximately 70% of patients whose tumors express estrogen receptors, 5 years of anti-estrogen therapy with tamoxifen will be recommended. Although this treatment can potentially be delayed for childbearing, at this point, the optimal regimen is to complete a 5-year course, during which time pregnancy should be avoided. These treatment issues underscore the importance of early discussion about fertility preservation in the establishment of a patient's management plan and the significance of a team of caregivers who are knowledgeable and available to provide the care necessary to allow for the treatment of breast cancer in conjunction with fertility preservation.

## Case #1: A Young Patient Who Refused Fertility Preservation

A 37-year-old female patient presented with a 2 cm isolated left breast mass located in the upper outer quadrant. The mass was palpable and appeared suspicious on ultrasound, mammogram, and MR imaging. Ultrasound-guided core biopsy of the lesion was performed and the pathology revealed estrogen (ER)-, progesterone (PR)-, and human epidermal growth factor receptor 2 (HER2)-positive disease. The patient was a high-level business executive and competitive athlete. At the patient's initial consultation, she was very anxious to arrange a surgery date. She was interested in the option of breast-conserving surgery with post-operative radiation therapy, which would allow her the quickest recovery time so that she could return to her athletic training. In light of her HER2-positive diagnosis, treatment with chemotherapy was also indicated. Prior to the end of her initial visit, the issue of fertility preservation was discussed with the patient and her husband. The patient said that she was not interested in fertility preservation, stating that she wanted to focus on beginning her cancer treatment and returning to her athletic goals. Subsequent to the patient's first surgery, she was found to have axillary nodal involvement requiring an additional operation. During the consultation for this second surgery the subject of fertility preservation was again addressed with the patient and she refused. Additional counseling with an oncofertility patient navigator was offered, but the patient declined. Subsequent to the patient's second surgery, she began treatment with chemotherapy. Eight months after the initiation of the patient's cancer treatment, she and her husband returned to the surgery clinic for a follow-up appointment. At this point, they stated their desire to start a family. Since the patient began treatment with chemotherapy, she had become amenorrheic. Additionally, she had six additional months of bioimmunotherapy with herceptin remaining in her treatment course, during which time it would not be considered safe to become pregnant or undergo fertility preservation techniques. At the completion of the patient's herceptin treatment, the patient returned to the clinic for follow-up and remained amenorrheic. She stated regret at not pursuing fertility preservation options prior to the initiation of her cancer treatment. In a few weeks, she was scheduled to begin 5 years of treatment with tamoxifen, during which time pregnancy was also not recommended. At the completion of her tamoxifen therapy, the patient would be nearly 43 years old. She was not comfortable waiting any longer to begin a family and planned to delay treatment with tamoxifen to pursue fertility treatment.

This case highlights the importance of early intervention regarding fertility preservation before the patient begins treatment with systemic therapy. If this opportunity is missed, the potential for the patient to have a biologic child may decrease significantly. Ideally, the patient should meet with two separate experts well versed in fertility preservation options prior to the initiation of treatment, though this may not always be possible to facilitate. It is crucial to be supportive of the patient through the treatment process. Should the patient change her decision regarding her desire for a family, within the framework of the patient's established treatment plan, appropriate counseling should be arranged to help support the patient's wishes.

## Case #2: A Young Patient Who Desired Fertility Preservation

A 34-year-old female patient presented with an isolated 3.5 cm, firm left breast mass visualized by ultrasound, mammogram, and MRI. Core biopsy of the mass was performed, and ultrasound detected a suspicious left axillary lymph node. Pathology of the primary tumor revealed hormone receptor-negative and HER2-negative infiltrating ductal carcinoma. The left axillary lymph node was also found to be positive for malignancy. Treatment options discussed with the patient and her husband included: timing of chemotherapy, breast conservation versus mastectomy with left axillary dissection, and the use of radiation therapy. The patient opted for primary surgery followed by chemotherapy. The issue of fertility preservation was also discussed, and the patient, who already had two children, strongly expressed her desire for another child.

Shortly after consultation with the surgical oncologist, the patient and her husband met with an oncofertility patient navigator. The patient's case was then presented at multidisciplinary oncofertility rounds attended by the oncofertility team, which included the patient's oncologists, a reproductive endocrinologist, and the patient navigator. During the year prior to the patient's diagnosis, her baseline FSH was found to be 5.0 mIU/ml. The patient then met with the reproductive endocrinologist who discussed fertility preservation options including embryo cryopreservation, oocyte cryopreservation, and ovarian tissue cryopreservation. The patient opted for embryo cryopreservation and was started on oral contraceptive pills due to the early timing of her menstrual cycle at the time of the consultation. She then underwent surgery for her breast cancer and was found to have locally advanced disease. During her 4-week recovery, she completed successful ovarian stimulation and oocyte harvest resulting in the cryopreservation of five embryos. Without any delay in the management of her cancer, the patient then began treatment with chemotherapy. During the patient's treatment, she often stated that the knowledge that she had preserved her fertility helped her persevere through treatment and served as a great source of comfort to her. Two years after the completion of her treatment, the patient and her husband began thinking about having another child using the patient's banked embryos [2].

This case highlights the relative ease of implementing fertility preservation into the care of breast cancer patients. Critical factors to the success of this practice include early discussion with the patient regarding fertility preservation, patient interest, and establishment of a multidisciplinary oncofertility team that is available to see patients on short notice and is flexible about scheduling visits and procedures in concert with the cancer management plan. Concerns include the reconciliation of a poor prognosis known prior to the initiation of fertility preservation and future plans to have a child in the face of an uncertain life expectancy.

## Conclusion

Newly diagnosed young breast cancer patients are faced with several complex decisions regarding both cancer care and fertility preservation during a time of tremendous stress. Patients are often unable to process the impact of a new cancer diagnosis on their fertility at the initial oncology consultation. For this reason, it is critical that the physicians who care for this young cancer population are sensitive to the unique issues inherent to this patient group. It is difficult to predict which patients who initially refuse fertility preservation counseling will have a change of heart subsequent to the initiation of systemic therapy. Counseling must be offered early in the treatment process and on separate occasions to ensure that an appropriate effort has been made to educate the patient about her options. These discussions should be well documented by the health care team members involved.

Ethically, determining how aggressively to pursue the counseling process is challenging. The patient's health care team can never be sure that the patient understands all the risks and benefits of her treatment plan, regardless of how many consultations take place. Furthermore, it is ethically challenging to discern if fertility preservation should be offered to breast cancer patients with a known poor prognosis. The implications of producing reproductive material, primarily as a symbol of hope for poor prognosis patients, are far reaching. Just the same, this provision of hope may be a key factor that helps young patients sustain their sense of identity through such a difficult life event. The best practices to capture those patients who will ultimately desire biologic children are actively being examined. Additionally, the appropriateness of patient selection for fertility preservation is also being considered. Currently, fertility preservation counseling is being offered to all patients who are under 45 and to anyone who expresses an interest.

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# Chapter 36
# Warning: Google Can Be Hazardous to Your Health: Fertility Preservation Is an Important Part of Cancer Care

**Jennifer Hirshfeld-Cytron**

As a resident, I had the opportunity to take care of a young woman with an ovarian germ cell tumor. She initially presented to an outside facility with an ovarian cyst believed to be benign. Following a cystectomy at this facility where the frozen pathologic specimen was determined benign, the final pathology unexpectedly returned as malignant. She then presented to the University of Chicago oncology service for a second opinion. She underwent conservative surgery with unilateral salpingo-oophorectomy and lymph node sampling, and the contralateral ovary and uterus were grossly normal and preserved. This fertility-preserving surgery is standard of care for women with germ cell tumors confined to one ovary that have not completed childbearing. She was to return to the inpatient chemotherapy service for her BEP (bleomycin, etoposide, and cisplatin) regimen following recovery from the surgery.

During the inpatient post-operative period, I discussed with her the topic of fertility preservation. As a senior resident with plans to pursue a fellowship in reproductive endocrinology and infertility, I was excited to have these discussions with patients. Fertility preservation was routinely discussed in the germ cell tumor population in regards to surgical options. Upon our discussion, I quickly learned two things about my patient. Although I thought the idea of fertility preservation would be novel to her, she had not only thought about it but also generated a plan. She demonstrated an incredible maturity for a 20-year-old girl. She promptly told me without even so much as a pause, "I have thought about it and plan to adopt." Presumably, my patient had assumed that the removal of her ovary and subsequent chemotherapy would render her infertile. Yet, following conservative surgery and chemotherapy for germ cell tumors, at least 80% of patients will have conserved reproductive function depending on their stage of disease [1–3].

My patient, although savvy, had received the wrong information. She needed to be reassured about her fertility prognosis given her current cancer therapy. I was reminded of the need to have discussions with patients regarding future fertility and

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ask the necessary questions, even if the patients seem knowledgeable. The false security the medical profession feels when patients do not inquire is dangerous in that it leaves our patients relying on alternative sources for their information. Fertility preservation discussions can occur at all levels of our health care system from nurses to medical students to residents to fellows as well as attending physicians. As a current reproductive endocrine fellow, I hope to pass on this lesson to those clinicians currently on the front lines of cancer care.

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# Chapter 37
# The Role of a Patient Navigator in Fertility Preservation

**Jill Scott-Trainer**

As the patient navigator for the Department of Fertility Preservation at Northwestern University, my main concern is the overall emotional well-being of the patient. I have spoken with over 300 patients who have had a recent cancer or autoimmune disease diagnosis. Finding out that you have a life-threatening illness is horrifying, and patients have told me of the emotional rollercoaster that they experience when they are first diagnosed. Many patients will not even think how their treatments may affect their fertility. Likewise, it is not necessarily the first thought on their surgeon's or oncologist's mind either. This is not surprising when the first priority is to save the patient's life. When facing a life-threatening illness with unknown costs, trying to make a decision about their fertility may not be a priority for some patients. However, preserving fertility is important for many patients and should always be discussed regardless of prognosis or income.

When talking with patients, I try to give them the full spectrum of options, including the option of not doing anything to preserve their fertility. Although not all treatments will affect fertility, the type of chemotherapy, dosage, and age of the patient are all things that need to be taken into account on an individual basis. It is hard to know with absolute certainty whether the treatment patients receive will eliminate their fertility, as each individual responds different to the impact of cancer treatment. Sometimes the initial course of treatment may not cause any risk to a patient's fertility but if the patient does not respond to this treatment, a more aggressive regimen may begin immediately. This is why it is critical to discuss fertility preservation when the patient is first diagnosed. In many cases, patients view fertility preservation as an insurance policy, a preventative health measures to protect the potential to parent.

My role as the patient navigator is to serve as the patient advocate, explaining the impact of cancer treatment on fertility, outlining the options available to each

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patient, helping the patient schedule appointments and navigate the health care system, and offering supportive counseling if the patient is in need. In my experience, the typical patient is female, recently diagnosed with breast cancer, in her late twenties to early thirties, newly married or in a committed relationship, and knows that she wants to preserve her fertility. When discussing her options, I break down the conversation into three categories: having biological children, using an egg donor, and adopting. Patients who are given the time can undergo an egg harvest that takes about 2 weeks (timed with her menstrual cycle) and freeze either embryos (if the patient has a partner) or unfertilized eggs (experimental research protocol). If the patient does not have the time to undergo an egg harvest, I discuss ovarian tissue freezing, an experimental research protocol where one ovary is removed and the resulting ovarian tissue frozen for later use. If the patient has the time and the resources to have an egg harvest, this is her best option to have a biological child in the future, as ovarian tissue freezing is still considered an experimental procedure. Aside from time, cost can be another factor that influences patient’s decision making, and in my role as patient navigator I outline the expenses for each procedure and help patients understand insurance coverage and out-of-pocket expenses for each option.

Men have a number of advantages when it comes to fertility preservation. They can bank sperm (which can be scheduled quickly) by making an appointment with a sperm bank. Fertility preservation costs are lower for men, although cryopreservation and storage fees are generally not covered by insurance. Although fertility preservation for men may be more straightforward, these cancer patients still require counseling and support in the decision-making process. As the patient navigator, I also assist male cancer patients, addressing their fertility preservation concerns and guiding them through the medical system.

Two key points that need to be considered when counseling fertility preservation patients are time and money. How much time is the oncology team willing to give the patient to preserve his or her fertility? Can the patient afford any of the possible options? For the patients that I have consulted, cost is almost always the deciding factor. Fertility preservation can be very expensive, especially when the patient is already burdened with large medical bills for their cancer treatments. Many patients, male and female alike, do not have any coverage for fertility preservation so it becomes an out of pocket expense that can run up to $15,000 (one IVF cycle plus the cost of medication). Some centers have discounted prices and are willing to arrange payment plans with patients. It is unfortunate that cost keeps many patients from preserving their fertility, but this is the reality, and my job is to make sure patients understand their options and the costs associated with their medical decisions.

My goal is to give patients information on fertility preservation as soon as possible, thereby allowing them to make an informed decision about their future fertility.

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# Chapter 38
# Judaism and Reproductive Technology

**Sherman J. Silber**

## Introduction

Reproductive technology offers a bewildering number of options for infertile men and women to have children, including ovary and testis freezing, transplantation, in vitro fertilization (IVF), donor sperm, donor eggs, stem cells, gestational surrogacy, genetic diagnosis of embryos, and, of course, birth control. These technologies cut to the very core of personal and religious belief systems. The purpose of this chapter is to explain the approach of classic Jewish Law to these technologies and how I see my work within it.

Judaism as a religion today is not well defined. While Jews are a common people, the religion of Judaism is divided into three main branches: "orthodox," "conservative," and "reformed." Approximately about 10% of Jews worldwide are orthodox, and orthodox Judaism is the only branch that is quite well defined (National Jewish Population Survey 2000–2001). Approximately 70% of Jews worldwide are reformed or "secular." About 20% of Jews are conservative, which is a sort of a hybrid between orthodox and reformed Judaism. With the exception of orthodox Jews (10%), most Jews would have a very difficult time defining their belief system. In fact, orthodox Jews often define themselves as "religious" Jews so as to distinguish themselves from the other 90% (reformed and conservative) who are viewed by the orthodox as ethnic and historical Jews, but who are not following the traditional Jewish religion. Thus, to simplify the discussion of Judaism and modern reproductive technology, it is much easier to concentrate on this more clearly defined orthodox branch of Judaism since it has the most severe set of rules.

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## Basic Tenets of Orthodox Judaism

The basic and unshakeable tenet of Judaism (prior to the reform and conservative movements in the last century) is that the Torah is the revealed word of God handed down at Mount Sinai 3500 years ago and witnessed by 600,000 people [1]. The "written Torah" refers to the first five books of both the Jewish and Christian Bible. Judaism believes that its basic responsibility is to transmit reliably to each succeeding generation the fact that God appeared to 600,000 people on Mount Sinai, so that no single person could claim that he/she had an exclusive revelation from God [2]. Rather, the entire nation of Jews observed it, and therefore no one could have simply been making it up. Judaism believes that it is not unreasonable to assume that what was witnessed 100 generations (3500 years) ago was so important in the lives of these desert nomadic people that it has been transmitted accurately through the millennia from parent to child and represents the absolute truth of what God expects of us [3]. In fact, the word "Torah" literally means "instructions for living." The orthodox Jewish view is that life is so complex, challenging, and confusing, that without such a "handbook," like an instruction manual, it would be impossible to know how to live life in the best possible way. That is why, 3500 years ago, after Noah had discovered the principles of moral behavior, and after Abraham had discovered the universal validity of monotheism, the world was finally ready for the very specific revelation of the law on Mount Sinai after the exodus from Egypt [4].[1]

The "Torah" consists of the classical "written" Torah, which is the first five books of the Bible, i.e., the five books of Moses and the "oral" Torah, which is the "Talmud." The Talmud contains the directions that were also given on Mount Sinai to the "children of Israel," but which were too cumbersome and laborious and too subject to subtle interpretation to be allowed to be written down [5]. In fact, the oral Torah continued to be added to by religious scholars, rabbis, and sages over the last 3500 years in the form of legal opinions and disagreements regarding the interpretation of the commandments. Thus, the Talmud consists of rules that were considered to be an oral expansion and clarification of the written Torah, which is composed of the arguments and views and opinions from sages down through the centuries [6].

In early Judaism, it was felt that the oral Torah must not be written down because the very concept of oral Torah allows for re-interpretation of absolute rules and commandments according to new conditions as life changes with the coming centuries. Nonetheless, it was written down after the first century AD when it was feared by the

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[1] Universally recognized as one of the all-time greatest scholars of Kabbala, who completely penetrated its esoteric (and enormous) breadth, depth, and meaning. Perhaps most strikingly of all, he was able to synthesize and systematize his knowledge in a way that portrayed the grand design (and intent) of the creation, distilling it even into works suitable to the laymen such as "Path of the Just," "The Way of G-d," and "The Knowing Heart" (all available in English translation). These works outline a logically flawless understanding of the purpose of existence, the reason for good and evil, suffering, death, nature of the hereafter, and much more. That's why today they are regarded as basic texts for understanding Judaism.

rabbis of the time (after the Romans expelled the Jews from Israel) that it might be lost if it were simply left to being handed down orally as it had been in the previous 1600 years.

The basic tenet of orthodox Judaism is that this written and oral Torah contains a complete guide as to how God expects you to live your life. It is critical that you follow these commandments and it is critical that when there appears to be conflicts or ambiguities in these commandments, that you use all of your intellectual ability to try to discern from these ambiguities and conflicts what exactly it is that God meant for you to do in every single situation that comes up in your life [7].

## Orthodox Jewish Legal System

The orthodox Jewish legal system can be viewed as an extraordinary exercise in deductive logic and can be compared for the sake of clarity to "Euclidean" and "non-Euclidean" geometry. Euclidean geometry, which we all studied in high school, is not just a math course about shapes and lines. It is a study in the concept of deductive reasoning. In Euclidean geometry there are a set of 6 axioms and 19 postulates, which are basic "obvious" truths from which the entire geometric structure of the world was derived. For example, one of the six axioms is that the "total is equal to the sum of its parts." Axioms are basic truths that are not specific to geometry but to math in general. Postulates are basic truths that are specific to geometry. An example of 1 of the 19 postulates is that "the shortest distance between two points is a straight line." From these basic axioms and postulates, which no one would argue represent basic general truths, the entire system of Euclidean geometry (involving areas of triangles, squares, polyhedrons, and circles) is derived. A complex system whose truth seems incontrovertible could be constructed using deductive logic from these very simple sets of axioms and postulates.

In the same way, the Jewish legal system was derived via deductive logic, extrapolation, and argumentation based on the basic commandments in the Torah that were considered incontrovertible and irrefutable axioms and postulates. The result was a legal system that encompasses every imaginable detail of what one should and should not do based on God's primordial directions to mankind from Mount Sinai [1, 7].

However, Euclidean geometry (as logical and unassailable as it appears to be) has rather unexpected potential deviations if just 1 of those 19 postulates is challenged. For example, the nineteenth Euclidean postulate states, "Only one line can be drawn through a point which is parallel to another line." This postulate seems to be pretty obvious. But in the nineteenth century, a completely different system of geometry based on the world being curved rather than a rectangular structure assumed that through a point, any number of parallel lines can be drawn parallel to any existing line. This "non-Euclidean" system of geometry was the basis for much of Einstein's computations of relativity. It is this "risk" that any of the commandments (like postulates) might have been misinterpreted that in Judaism requires constant study, review, and argumentation. The orthodox Jewish legal system supports a constant questioning process as the only way to attempt to approximate the truth, which orthodox Jews do believe ultimately derives from Torah [5, 6].

Lest one misconstrue that orthodox Judaism is simply a very complex system of rules and regulations based purely on left brain rationalism, it is also an orthodox Jewish concept that by intensely studying, and indeed intellectually questioning, the rules which are derived from the many commandments of the Torah, in an effort to be as certain as possible that we are following God's directions properly, one gets closer emotionally to God [4]. At this point, a feeling of spiritual exhilaration and absolute faith evolves from what was otherwise a purely cerebral endeavor. So despite Judaism's goal as a purely logical religion that transcends the irrational leap of faith, there is still room for the irrational and impulsive when difficult matters come up.

## Major Jewish Themes

The major themes throughout Judaism are that God is one, that life has a purpose, and that purpose is to live a good and moral life [1]. However, life is very confusing and filled with potential conflict. Therefore, the essence of orthodox Judaism is that only through intense and relentless study involving argument and counterargument via logic and extrapolation, can Jews be guided through this confusion into leading the proper life [7].

Therefore, the orthodox Jewish essence is that one must study Torah from the earliest years with all of their intellectual might. The purpose is to try to figure out through logic and introspection, debate and counterdebate, all based on Torah, what it is that God expects of us. Only through critical study of Torah can orthodox Jews figure out how to manage every single detail of living [6].

## The Most Important Two Commandments

The first commandment to appear in the Torah (and of course also in the Christian old testament bible) is that mankind should be "fruitful and multiply." As a corollary, the next commandment is that human life should be preserved above all. For example, if all there is to eat is pork, and otherwise you would die if you did not eat the pork, you are commanded to disobey the injunction against eating pork, so that you can continue to live. The only thing you are not allowed to do to save your life is either to deny the existence of God or to cause someone else to die [7]. Every other law can be forsaken if otherwise you would die. To either kill yourself or allow yourself to die unnecessarily, or to kill someone else, is strictly forbidden because the most important tenet in orthodox Judaism is that human life is to be preserved above almost all other laws.

Other examples of Jewish law are that you must say a blessing over every meal and over every single pleasure so as not ever to take anything for granted. The reason for the commandment to say blessings is not because God needs to receive our thank you. The reason that God gives the commandment to say blessings is so that our pleasure in life can be enhanced by never taking the preciousness of life for granted. For example, you must thank God whenever you wake up in the morning for "renewing" your life. You must even remember to say a blessing over your sphincter whenever you are finished going to the bathroom. This may sound humorous and always gets a giggle from the audience. But just think about it. We take our sphincter for granted, unless we have an ileostomy or incontinence. As we walk around and live our normal lives, we do not derive any true joy from appreciating how wonderful it is that we have a properly functioning sphincter, unless we remember to say a blessing every time we finish going to the bathroom.

## Confusion Which Can Result from Attempting to Follow the "Commandments"

It is well known that Jews must not do any work on the Sabbath so as to remember and be grateful for the creation of the universe [8]. The Sabbath is considered very holy because it is a celebration of our very existence, and it is the most important holiday in Judaism, occurring every single week on the seventh day, the day that God rested from creating the universe. Keeping the Sabbath holy is one of the most important and unassailable commandments in Judaism. That is the day that orthodox Jews interface most directly with God, by following the specific commandment not to do any work on the Sabbath. That sounds easy, but how do you define "work?" Rabbis and sages over the last 3500 years have continually debated this simply to try to figure out what is and what is not work that is or is not allowable on the Sabbath [6, 8].

For example, driving your car, even to Synagogue or anywhere else on the Sabbath is considered work. However, walking 20 or 40 miles on Sabbath, if you live that far away, is not considered work. Lifting a 50-pound weight inside your house is not considered work, but carrying a single feather outside your enclosed neighborhood, or outside of your house, is considered work which is not allowed on Sabbath. The mere flip of a switch, turning on a lightbulb is considered work, whereas serving a meal to 40 guests is not considered work [8]. This is the type of confusion that can result when one sincerely attempts to follow the simplistic commandments of the Torah without having committed oneself to detailed and scholarly questioning. The logical answer has been to consider whatever was not allowable on Sabbath during the building of the tabernacle by Mount Sinai to be defined as work. Driving a car or turning on a light is considered work because it is the equivalent of starting a fire. Carrying a feather outside of the neighborhood is considered work because transporting from one area to another is not allowed, but rearranging furniture or other items in your house is not considered transport and is not prohibited in the Torah [8].

What is the point of giving these examples of the difficulties that the most religious Jews have in deciding what actions do or do not conflict with what God expects of us? It is to point out that the orthodox Jewish views toward IVF and modern reproductive technology (like the Sabbath) have been subject to relentless intellectual scrutiny by some of the most brilliant minds in Judaism, attempting to extrapolate from ancient laws believed to be handed down directly from God, what is and what is not allowable.

## Infertility, IVF, Embryonic Stem Cells, Ovary Transplantation, and Judaism

The Jewish views on IVF and modern reproductive technology issues are therefore readily deducible. According to the Talmud, the soul does not enter the embryo until 40 days after conception. Furthermore, we all have an obligation to have offspring and to "be fruitful and multiply." IVF is absolutely obligatory when it is medically indicated in order for a couple to have children. It is not just allowable, but it is obligatory. Preimplantation genetic diagnosis (PGD) represents no moral or ethical risk, because the soul has not yet entered the embryo. Selective reduction of a multiple pregnancy is acceptable if its goal is to enhance the possibility of life.

Embryo research to promote life is, therefore, acceptable. Not only is therapeutic cloning acceptable but it is an obligation to do any research which can enhance and promote life-saving treatment such as stem cell and cellular replacement therapy. In orthodox Judaism, which is otherwise a "right to life" and anti-abortion religion, the early embryo does not yet have a soul and so is *not* yet a person. Nonetheless it cannot be just discarded for no reason, because it is a step toward the commandment "be fruitful and multiply." But it would not be considered murder to utilize an early embryo for research that might eventually save lives.

## Commandments in Conflict

The Talmud specifically forbids "cutting the sperm ducts" [9, 10]. But yet the Torah insists "be fruitful and multiply." So if we are not allowed to cut the sperm ducts, and yet we are obligated to do whatever we can to have children, what about "MESA" and what about "TESE (i.e., microsurgical sperm retrieval procedures)?" These are procedures that allow us to retrieve sperm from men who are otherwise sterile, in order to perform IVF and give them children. Modern Talmud scholars, universally respected orthodox Rabbinical minds, have weighed this conflict and decided that the first commandment "to be fruitful and multiply" takes priority over the commandment not to "cut the sperm ducts." Therefore, MESA and TESE are fully allowable and, in fact, mandatory (Rabbi Y.S. Eliyashiv and Rabbi Dovid Morgenstern, 2009, oral decision, Personal communication).

Such a decision, based on a clear conflict between two commandments is referred to as a "leniency." In other words, the rabbis are not really happy about the prospect of an apparent violation of a Torah commandment, but it is understood that God's intention in the commandment to avoid cutting the sperm ducts was meant to be a corollary of "be fruitful and multiply," and not to be a prohibition against doing whatever you can to "be fruitful and multiply." Nonetheless, because it is just a "leniency," once the couple has had a boy and a girl, they are not allowed to have any further sperm retrieval procedures which would "cut the sperm ducts." For this reason it is important that the first such procedure on any orthodox Jewish couple retrieves and safely freezes all the sperm they will ever need for as many future babies as they might wish to have.

## Controversial Issues Such as Donor Gametes

Most rabbinic authorities forbid either egg or sperm donation (Rabbi Y.S. Eliyashiv and Rabbi Dovid Morgenstern, 2009, oral decision, Personal communication). The reason is that Jews are commanded "to build a wall" around the sacred marital bond. Women cannot even touch via handshake another man. The same is true of course for men, who cannot even shake the hand of another woman, unless it is his wife or blood relative. Also men and women must dress modestly so as not to invite any sort of flirtatious breach of that marital firewall. However, what if the only way to fulfill the first commandment, "be fruitful and multiply" is donor gametes?

The great legal orthodox Jewish minds are very cautious on this issue. Many orthodox Jews assume that donor gametes are not allowable and do not even think to engage in detailed, syllogistic scrutiny of this issue. Therefore, most rabbinic authorities generally do not allow either donor sperm or donor eggs. There is no clear injunction in the Torah against donor sperm or donor eggs, and there is a clear imperative to "be fruitful and multiply." In fact, the imperative to "be fruitful and multiply" is so strong that prior to modern reproductive technology, divorce (which is generally shunned among orthodox Jews) would be allowed if the couple were infertile, just to allow them the chance to try via a different marital partner to have children.

One way for the couple who needs donor gametes to solve this issue is to search "for the right rabbi" who will go through the details of this complex issue with them privately and perhaps favorably. The issue is complicated and complex, and one of the greatest conflicts in all of orthodox Judaism arose out of this issue. The most respected orthodox Jewish mind of the twentieth century was Rabbi Moshe Feinstein (1975, oral decision, Personal communication). Unfortunately he passed away, but his views (however, radical seeming) were generally regarded by orthodox Jews, no matter what their hesitation, as the correct guidelines. His knowledge and his reasoning were considered to be vaster than any other rabbi in the later twentieth century. He never had a chance to make a ruling on donor eggs, but he felt the use of donor sperm was a private matter for the couple to decide, and in certain situations it would be recommended in order to fulfill the first commandment as well as to keep the marriage together. Despite his favorable opinion, there is a universal sentiment among most orthodox rabbis against any use of donor gametes. When you press the rabbinic students on why there is this almost universal disagreement on this one issue with the otherwise unassailable Rabbi Moshe Feinstein, they answer that sperm donation is just going too far. Despite his great logic, and despite Judaism's emphasis on rationality, most of the great rabbis today simply do not accept Rabbi Feinstein's favorable ruling on gamete donation.

## Ovary (and Testicle) Transplantation

Ovary (and testicle) transplantation solves this dilemma of gamete donation for orthodox Jews and is very helpful for physicians to understand when counseling patients with ovarian failure who cannot have egg donation for religious reasons. Ovary transplantation is currently an important tool for orthodox rabbis' in helping women with premature ovarian failure as well as for cancer patients who are candidates for fertility preservation. Our work in this arena began with a series of discordant identical twins (one had no eggs at all and the other had two normal ovaries and was quite fertile), we transplanted ovarian tissue from the fertile twin to the sterile twin, and in all cases normal reproductive function ensued, with all natural conception and pregnancy following. So far frozen ovarian tissue has performed as well as fresh. Freezing ovarian tissue in cancer patients who will otherwise be rendered sterile from their treatment is the current technology at the center of our effort to preserve the fertility of young women so that they can have biological children. Transplanting this tissue back to the same woman does not seem to raise any objections within Judaism. But what about transplanting tissue from one woman to another who is in ovarian failure in lieu of egg donation?

The most severe orthodox rabbis fully approve of this approach to gamete donation (Oral Decision – Eliyashiv and Morgenstern, 2009, Personal communication). Although egg donation is not allowed, ovary tissue donation is allowed. Neither the rabbis nor the patients are fooled into thinking that the DNA of the child comes from anyone but the donor. There is no delusion on that point. They know full well that from a genetic point of view, this is no different from egg donation. However, from a spiritual perspective, the egg is being ovulated within the body of the intended mother and that makes all the difference. The DNA is not the major issue with gamete donation, but rather the possible intrusion past the safety firewall that orthodox Jews must build around the sanctity of the marriage. So as long as the ovulation is taking place inside the wife's body, ovarian tissue transplantation is consistent with the severest Jewish law, even if the DNA is not hers. The soul of the baby does not enter until approximately 6 weeks of fetal life, and therefore is in a sense independent of the DNA.

## Torah and Science Do Not Conflict

Even the most fundamentalist orthodox Jewish viewpoint maintains that Torah and science do not conflict. Humankind must use its creative intelligence to resolve conflict and to figure out from the "basic" principles of Torah what is right and never to be blinded by dogma. A good example is the orthodox Jewish view of creation and the concept of the big bang. Most physicists today believe that the universe is approximately 13 billion years old. That would seem to conflict with the biblical notion that the universe was created in 6 days, and on the seventh day, God rested. However, MIT physicists have studied this concept of the Big Bang mathematically using basic principles of the relativity of time and velocity popularized by Einstein.

As an object is proceeding at or near the velocity of light, time slows down dramatically in relation to a fixed observer. Einstein originally postulated that if you were to travel in a spaceship at the speed of light for thousands of years and then return to earth, you will not have aged significantly, but back on Earth it will be thousands of years later. Time simply gets slower the faster your velocity in relation to a fixed observer. If God and the universe are considered one, a basic Jewish postulate, and the universe is expanding near the speed of light, then the 13 billion years which astronomers measure as the age of the universe mathematically comes out for God to be approximately 6 days. Thus, there is no conflict between our observation that the universe is approximately 13 billion years old, and the traditional biblical view that the universe was created in 6 days. This is one example of the firm belief in Judaism that science, observation, and study do not, and should not conflict, with religion and spirituality. That is not considered to be God's wish. The orthodox view of the most respected rabbinic minds is that Torah should be a window to view the universe with an open mind and should not be a wooden shutter.

Thus, the strictest orthodox Jewish theology maintains that the Torah is not in conflict with reproductive technologies. In fact, it is actually a religious obligation for orthodox Jews to preserve their fertility and their ability eventually to "be fruitful and multiply." For cancer patients of reproductive age, Jewish law ultimately requires every effort to safeguard the possibility for future parenthood.

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# Chapter 39
# Reading Between the Lines of Cancer and Fertility: A Provider's Story

**Leonard S. Sender**

As oncologists with experience in the growing area of oncofertility, there are some standard elements we think of with new patients in regards to oncofertility, such as sperm donation, egg harvesting, ovarian cryopreservation, cost of the procedures now and in the future, and cost of storage. We try to think of everything to tell our patients – all their options, the benefits and risks, and the odds of various outcomes. And while we know the issue is monumental for our patients, we can sometimes lose sight of the lifelong impact of their cancer and oncofertility decisions, and the myriad of ways these decisions will shape their lives and manifest themselves in surprising ways unique to each patient. We can also forget that the discussion of oncofertility itself may create an issue for a patient with which he or she might not otherwise have struggled.

A good example is a former patient of mine. When I met Samantha[1] in mid-2002, she was 26, had just started a new job, and was engaged to marry that fall. The circumstances that led her to me began as it does for many of our young adult patients. Nearly 2 months earlier, she went to a walk-in medical clinic complaining of a nagging sore throat and tiredness. There, she had some blood work done that looked a bit unusual, so she was sent to an internist. The internist did more blood tests, which showed a high white blood cell count and low red blood cell and platelet levels. He ordered a bone marrow test and told Samantha that while waiting for the results, she should schedule an appointment with an oncologist, just in case. The day before her scheduled oncology appointment and 10 days after the bone marrow test, the internist called her at work to tell her that the test had revealed that she had acute myeloid leukemia (AML). At her appointment the next day, the oncologist told her that he primarily worked with breast cancer patients and since her diagnosis was AML, he advised her to see a hematologist/oncologist instead. He told her that he just happened to know someone across the street at a different medical center he

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[1] The patient's name and other identifying details have been changed to protect her privacy.

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thought she should see. He then called my staff and Samantha came over shortly after.

When Samantha arrived in my clinic that June day, she was already so sick that I told her she would have to be admitted immediately and that I wanted to conduct my own bone marrow test, under conscious sedation, to confirm the diagnosis and evaluate more extensive prognostic indicators. There was no time to delay or, as she asked, go home first to pack her favorite pajamas and other personal items. A few hours after the test, the diagnosis was confirmed (a drastic comparison to the 10 days it took the internist to tell her the results). She required 4 units of packed red blood cells when she was first admitted, and later that night she had a central line put in and began chemotherapy.

Thus began Samantha's initial 6-week hospitalization and two rounds of chemotherapy to force her leukemia into remission. During this time, she celebrated her 27th birthday. We talked a bit about her having children in the future. I told her that it was unlikely she could carry a child of her own because of the chemotherapy and that there were not really any fertility preservation options for leukemia patients. At the time she seemed rather untroubled by the loss of her fertility, having told me that even before her diagnosis she and her fiancée had been undecided about having a family and now she was simply happy to be alive. In the midst of various hospitalizations and chemotherapy, Samantha got married. At the suggestion of one of my staff members, she chose to get legally married that fall on the originally planned day and to postpone the ceremony until the following year, on what would be her 1-year wedding anniversary.

Samantha had her bone marrow transplant at the beginning of 2003. By the end of February, she was recovering at home and starting to feel better, and over the summer we took out her central line. That fall, I was honored when she asked me to be her first dance at her wedding. Shortly after returning from her honeymoon, she began working part time, slowly building up her strength, and working to reassemble the pieces of her life left strewn by the cancer. We talked about family planning more and I advised her to wait until she passed the 5-year mark, when her odds of recurrence would drop dramatically. As she and her husband had always been fairly ambivalent about children, she seemed content to delay thinking about it.

As Samantha later would say, she figuratively held her breath for those 5 years. In addition to delaying dealing with fertility issues, she put off processing most of the other emotions and events related to the cancer as best she could. Some issues, however, she could not ignore. The chemotherapy induced the onset of menopause with the hot flashes and other side effects that come with it. Her desire for sex had all but vanished, not only a trying situation for a newlywed but also devastating to her personally.

In June of 2007, Samantha passed the 5-year mark and celebrated with a trip to Hawaii with her husband. Upon her return however, with the wall of the 5-year mark now removed, all of the grieving, emotions, issues, and questions that she had put off the past 5 years came over her like a tidal wave. She told me how she mourned the loss of the second half of her 20s to the cancer, lamented that she would never feel as secure in her health again, and grieved for the effect the cancer and its aftermath had wrought on her marriage and sex life. She also began to question why she had lived when so many of her friends from chemotherapy had not – was there some purpose to her surviving? Was it to have a family and be a mother?

I referred her to a fertility specialist, who explained to Samantha that her options were either to use donor eggs or to adopt. Her sister offered to donate eggs, but Samantha struggled with what it would be like to bear a child that she knew was genetically her sister's – what if the child looked more like her sister than herself? How would her sister really feel toward the child? How would her husband feel? As it was, the fertility specialist was reluctant about this option as her sister was 35, saying he would prefer Samantha to use a donor in her 20s, a possibility that raised a host of other doubts and questions for her. While she was initially reluctant about adoption, Samantha knew another patient who had adopted two children internationally and seeing her friend's experience had warmed her to the idea somewhat. During this critical decision point in 2007, Samantha and her husband determined that the only way they could afford the more than $20,000 it would cost to use a donor's eggs or adopt was to use the equity from their home (with the recent downturn in the housing market, that financial option is no longer available to them today).

Samantha came to see me, distraught and overwhelmed. She told me that she felt an inexplicable and overwhelming internal pressure to make a decision – to create some meaning out of her cancer because her sister was at the upper age limit to donate eggs, because her husband was 10 years older than she was, because she felt as though it was what everyone expected her to do, because everyone kept asking her about it. Unlike some survivors, she felt she did not struggle much with the long-term consequences and health implications of having a child, as she was too consumed with the more basic question of whether she even wanted to have children at all. In the midst of this, she was nagged by the question of whether she was focusing on this decision because of the cancer and the 5-year mark. Since she and her husband had been indecisive about having a family before her diagnosis, was she questioning her feelings about having children because they had now been married for a few years? Or, would they not even be thinking about having a family if she had not developed and then survived cancer?

I encouraged her to see a therapist and to begin to confront and process all these experiences, losses, and emotions she had put off for the past 5 years. While working with the therapist, she agreed to delay thinking any more about her fertility options for 4 months while she worked through her other emotions. Two years later, she still has not revisited the issue. Her wide social circle now includes a number of women, both married and unmarried, who are choosing not to have children, which has increasingly made her question if she really ever wanted children or if it was cancer that made children such an issue in her life. She has sought out other women who went through experiences similar to hers and talked with them about what decisions they made about family planning, how they arrived at those decisions, and how they felt about their decisions over time. Today, Samantha will not go so far as to say she has definitively decided against having children, but will say she does not plan to revisit the issue any time soon. She also still questions whether the compulsion she felt to have children after she passed the 5-year mark was truly how she would have felt regardless of the cancer, or whether it was driven by her perception of expectations from others or a need to make some sense of her survival.

Samantha's life was undeniably altered by her leukemia – her career is likely not what it would have been, their financial situation was negatively impacted by the extended time that both she and her husband did not work while she was sick and he cared for her, and, in what is perhaps the most persistent issue for her still today, she has expressed concern to me that her sexual drive is only beginning to approach what it once was. Samantha will also tell you that the cancer brought some wonderful things and people into her life and led to some experiences she feels certain she would not have otherwise had, including running a marathon.

Samantha's journey illustrates the complexity of being a young adult with cancer today. While fertility preservation is an amazing option we can now offer some cancer patients, having children is no longer a default expectation of becoming an adult, or even of getting married. Samantha's story is a cautionary reminder to all of us that every aspect of a cancer diagnosis and treatment influences the lives of our patients and when discussing all of the options a patient has, we must be careful not to assume the importance of fertility preservation and having children.

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# Chapter 40
# A Rewarding Experience for a Pediatric Urologist

Margarett Shnorhavorian

When I reflect on some of the most rewarding experiences in my practice, one of the most personally rewarding cases was on a fertility preservation consultation with a 12-year-old boy who had just been diagnosed with Ewing's sarcoma and told that the treatment would leave him infertile.

I got the page from his oncologist and I dropped everything to meet Tommy (fictional name to protect privacy) and his family in the oncology clinic. The room was quiet and the parents immediately impressed me as "salt of the earth" folks who were going to fight cancer with their son and wanted to make sure everything possible would be done for him. I introduced myself as an urologist and asked Tommy if he knew why I was there. He said, "Yeah, so I can be a dad someday." My eyes lit up as his description of my role was probably the best summary of what I do. It also reminded all of us in the room that Tommy was hopeful he would have a future beyond his cancer.

Based on Tommy's history and physical examination, I realized that he was not a candidate for sperm banking, but that I could perform testicular sperm extraction (TESE) while his line for chemotherapy was being placed in the operating room. Though thousands of TESE are performed every year in adults, Tommy would be the first TESE patient in our children's hospital. We had only recently started our fertility preservation program, so the next 24 h was spent coordinating surgeons, oncologists, nurses, the fertility lab, and the operating room. It was an elegant procedure, completed in 10 min. For good luck, I performed the "sperm dance" as taught to me by my mentors, in hopes of success as I handed off the tissue to the lab. The lab notified me that there was plenty of sperm and that the procedure was a success. It is often a challenge for me to explain to my 2-year old what I do as an urologist – but this time, when I came home I was beaming and said, "Mommy helped make sure a little boy could be a daddy some day!"

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# Chapter 41
# Final Thoughts

**Laurie Zoloth**

We live in a world so uncertain, so chancy, that we seek to fill it with certainty: fundamentalist truth, hard numbers, insurance policies, political correctness, regulatory schemes, IRBs, and tenure. But the truth is, nothing can save you from the loss at the heart of it all, the probability that you will wake, blinking, from a darkness you could not imagine, to a lit world you cannot expect. A fundamentalist politician can have a beloved gay daughter or a 15-year-old pregnant one, Wall Street firms can evaporate, you can lose your job, your house, America can lose wars, lose its cheerful, optimistic way. Nowhere is this uncertainty more terrifying true than in medicine, the tragic world to which bioethics attends. You can get cancer, your child can get cancer, and sickened and afraid, the choices you make just then will bridle or set loose the dark horse that is the future, and it will gallop off into parts unknown.

In this chancy world comes the scientist, and really, it is not her fault that she is so determined. Against the angst of the philosopher, and the desperation of the patients, and the exhaustion of the physician, the scientist must do her work, which is to try to reduce, just a bit, the sense of unknowingness, the mysterious blank undiscovered nature of the world. It is into this world, of chance and loss and uncertainty, that I was invited in early 2003. Teresa Woodruff, a scientist with a big idea, and little more, invited me to think with her about the ethical issues in infertility research, not for women seeking IVF, but for a certain population of women, women facing the mortality and morbidity of cancer who yet yearned to survive and bear children. These women faced a paradox: they had chosen to struggle toward a treatment for cancer, but it bore great risks. First, it might not work or only work for a time. Second, it would likely destroy or diminish their ability to bear children, as we used to say, and non-ironically, naturally. It was one of the first questions a scientist asked me to think about when I arrived at Northwestern and, certainly not tangentially, Woodruff was one of my first colleagues to want a new interdisciplinarity at the core of her research. She wondered: could ovarian tissue be frozen, stored, and

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then, years later, could the follicles be thawed and coaxed chemically to do what they do normally, which is to self-assembly the human oocyte? Could the egg be fertilized and become implanted in a women after cancer, to create a pregnancy and a child?

This book is the result of that colleagueship and of the official bioethics consultation project, later funded by the NIH in one of nine National Roadmap Grants. As the project grew in scope, I was invited to create a bioethics basic research project, into which I drew graduate students, undergraduate researchers, and entire undergraduate classes into the labs and the puzzles and the early dawn meetings of the doctors and scientists, the world of activist advocates, patients and families, from whom we came to learn. We invited other scholars from within the university and from other bioethics centers to come think with us, and several of them graciously responded, thus creating a national advisory board. A year later, we were joined by two gifted scholars who have helped create and edit this book.

This book is a collaboration of a new kind and a discussion of a new technology to allow for repair of a new problem. The collaboration is a discussion among research scientists, physicians, philosophers, theologians, legal theorists, social scientists, and historians at Northwestern University refers to emerging interdisciplinary efforts to bridge the fields of oncology and fertility studies in order to develop technologically driven medical solutions to the infertility cancer patients may experience as a result of their illness or its treatment. Techniques that provide women the option of preserving their fertility while deferring the choice of a sperm source until after the crisis moments of cancer diagnosis and treatment are of particular interest to oncofertility researchers. The Oncofertility Consortium takes a multi-pronged approach to expanding the role of fertility preservation as a factor for consideration in patients' treatment plans. These efforts include increasing patient and physician awareness of currently available fertility preservation options, promoting discussion of these options among patients and physicians, and attempting to develop new fertility preservation technologies so that more patients thinking about family planning in the context of a cancer diagnosis will have greater flexibility and options. Oncofertility researchers are studying cryopreservation technologies in order to improve methods for freezing and thawing ovarian tissue, immature ovarian follicles, and mature oocytes. Consortium researchers are also developing in vitro follicle maturation technology, which includes designing an artificial environment that mimics the ovary, in which immature ovarian follicles may grow into mature oocytes. Researchers hope that these oocytes may become an alternative source of eggs for women to use in current assisted reproductive technologies (ART), such as in vitro fertilization (IVF).

New technologies affect the societies in which they are utilized, and the social context of development and implementation also shapes a technology's reception and interpretation by members of society. Even the possibility of pursuing technological advances ought to prompt researchers and society as a whole to reflect upon the ways in which a new technology may change the society into which it is introduced and whether that change is morally valuable, permissible, neutral, or problematic. Oncofertility has the potential to affect societal conceptions of illness, cancer, family, suffering, mortality, and family planning. Consequently, Teresa Woodruff, Director of the Oncofertility Consortium, invited prospective ethical analysis of the fertility preservation techniques under development, in an effort to anticipate and preemptively attend to the ethical dilemmas and concerns that might arise during or due to the consortium's research. These ethical assessments may be informed by a variety of sources, including philosophy, anthropology, law, and psychology.

The work of bioethics, then, is a series of intricate, subtle questions. The book will raise only a selection of the many intense concerns we are raising, largely ones about the moral philosophy and ethics of the work at hand. The book represents a new sort of collaboration, in which bioethics has been a core part of the intellectual arc of the project since its beginning.

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