Published in final edited form as:

Cancer J. 2009 ; 15(1): 27–33. doi:10.1097/PPO.0b013e3181976602.

Medical and Psychosocial Aspects of Fertility After Cancer

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Abstract

Survival for cancer has improved significantly in the last 25 years with excellent overall 5-year and 10-year survival rates. Hence, the majority of young women diagnosed with cancer can expect to live for decades, making quality of life issues such as fertility increasingly important. Risks of infertility vary based on the chemotherapy and treatments employed, as well as a woman's age. In general, younger women are less likely to experience permanent amenorrhea than older women, but even women who continue to menstruate have a greatly increased risk of premature menopause. Options for cancer patients entering chemotherapy treatment who wish to preserve fertility range from clinically well-established techniques such as embryo cryopreservation to more experimental techniques such as ovarian tissue cryopreservation. Pregnancy does not appear to increase the risk of cancer recurrence. Discussion of fertility issues in premenopausal women diagnosed with cancer present important challenges to the provider and to the patient. However, failure to discuss these options adequately can have lasting negative consequences on a woman's quality of life. Physician education interventions should seek to improve the knowledge of fertility preservation options, and of locally and nationally available resources.

INTRODUCTION

Nearly 200,000 women between the ages of 20–49 are diagnosed with cancer every year. Fortunately, survival for cancer has improved significantly in the last 25 years with excellent overall 5-year and 10-year survival rates (79% and 74%, respectively) for all cancers in women in this age range.¹ Hence, the majority of young women diagnosed with cancer can expect to live for decades, making quality of life issues such as fertility increasingly important.

Many premenopausal women diagnosed with breast cancer today are still contemplating conception of their first child, or have not completed their child-bearing. Recent estimates from the Office for National Statistics have shown that the average age of women for all births in the US has gradually increased from 24.6 years in 1972 to 27.2 years in 2000.² In addition, the first birth rate for women between the ages of 40 and 44 years has more than doubled since 1981.³ A diagnosis of cancer at a young age threatens the developmental tasks that characterize a woman's reproductive years such as building intimate relationships and having children.⁴ ⁵ Young women diagnosed with cancer before the age of 50 experience greater psychological morbidity than their older counterparts,^{4, 6–9} with fertility issues among the most troubling of the issues they face.^{10–13}

RISKS OF INFERTILITY WITH CANCER TREATMENT

The risk of infertility with cancer treatments varies widely, and is dependent on the age of the patient as well as the types and combinations of treatment received.¹⁴ Difficulties with fertility increase with age and are much more common for women >40 years versus women ≤ 40.^{15–}

¹⁸ Unfortunately, there is no clinically useful predictive test to reliably assess ovarian reserve, ¹⁹ making it difficult to predict risk of amenorrhea for an individual woman. Table 1 reviews some common treatments for various cancers and the associated risks of amenorrhea on a population level.

Certain classes of chemotherapy agents are quite toxic to the ovaries, such as alkylating agents, which include cyclophosphamide and procarbazine,^{20, 21} and are frequently used cancer treatment regimens. High-dose chemotherapy administered in preparation for Stem Cell Transplant is also associated with high rates of ovarian failure.^{21, 22} There are a number of new chemotherapy agents for which data is lacking or not conclusive, such as the monoclonal antibodies, the taxanes, and tyrosine kinase inhibitors.²⁰ It should be noted that even women who do not experience ovarian failure immediately but continue menstruating after chemotherapy will have reduced ovarian reserve, and high rates of premature ovarian failure.^{16, 23}

Damage to the ovaries from radiotherapy is dependent on the dose, irradiation field, and the age of the woman.²⁴ The ovaries are exposed to significant doses of irradiation when radiotherapy is used to treat pelvic or abdominal disease, such as cervical and rectal cancer. Women aged < 40 years usually require 20Gy for permanent ovarian failure, while the dose is only 6Gy in older women.²³ In addition, whole body radiation, spinal radiation, whole brain radiation, and pelvic radiation combined with chemotherapy are associated with high rates of amenorrhea. Radiation to the pelvis also affects the uterus. Uterine radiation is associated with increased risk of spontaneous abortion, pre-term labor and low birth rate, likely due to changes in the musculature and blood flow from radiation.²⁵ Very young women are *more* susceptible to the damage from radiation to their uterus.²⁴

Surgical treatments that remove the reproductive organs, as in treatment of ovarian cancer, advanced cervical or uterine cancer, typically leave a woman infertile since standard treatment generally involves total abdominal hysterectomy with oophorectomy. However, depending on the stage and type of gynecological cancer, conservative treatment, which preserves the reproductive organs, can sometimes be attempted. Observational studies following women receiving conservative surgical treatment for cervical cancer suggest radical trachelectomy (which spares the uterus and ovaries), does not appear to increase the risk of recurrence or mortality when patients are early stage, properly screened for the procedure, and undergo surgery at a center experienced with performing the procedure.^{26–29} Women with early stage (stage I) and low-grade (I-II) ovarian cancer also appear to have no increased risk of recurrence when treated with conservative unilateral oophorectomy,^{30–32} although the potential for a second primary malignancy in the other ovary must be considered.³³ Women with early-stage (Stage I) endometrial cancer can often be treated successfully with a progestational agent, rather than abdominal hysterectomy. In fact, younger women with endometrial cancer tend to have better differentiated lesions and higher survival rates.³⁴ About three-fourths of women will respond to hormonal therapy, and those who do not can then proceed to more aggressive treatment if needed.^{35–37}

FERTILITY PRESERVATION OPTIONS

Several options for cancer patients entering chemotherapy treatment who wish to preserve fertility are available. The available options range from clinically well-established techniques such as embryo cryopreservation to more experimental techniques such as egg freezing and ovarian tissue cryopreservation.^{17, 38} Descriptions of these options are provided in Table 2.

Embryo cryopreservation is a widely established procedure that is commonly used in many infertility clinics around the world.¹⁷ It involves stimulation of the ovaries to produce eggs that can be fertilized by sperm and stored as embryos for future implantation and pregnancy.

Cumulative pregnancy rates can be > 50%.^{39, 40} The procedure can take from 2–6 weeks however, so it can delay the start of treatment. Women who have estrogen sensitive tumors are generally not considered candidates for traditional in-vitro fertilization (IVF) before cancer treatment because stimulation of the ovaries to produce embryos results in high levels of circulating estrogen. Alternative cycles using aromatase inhibitors, which result in lower circulating estrogen, are increasingly being employed in women who have hormone-sensitive tumors.^{41, 42} Women must have a male partner or be willing to use donor sperm for IVF, an important limitation. In addition, creation of embryos may conflict with moral or religious beliefs.

Women who can delay chemotherapy treatment for fertility preservation but do not have partners and do not wish to use sperm donation may opt for freezing mature oocytes. At a later date these oocytes can then be thawed and fertilization with sperm attempted. Success rates for fertilization of cryopreserved oocytes are much lower than for cryopreserved embryos and only several hundred offspring have been produced world-wide.^{38, 43} The mean pregnancy rate per thawed oocyte is low (1.5 – 4%) and the safety record for oocyte cryopreservation is not as extensive as it is for embryos.¹⁷ A recent meta-analysis suggests that pregnancy rates from oocytes are about one quarter the pregnancy rates achieved from embryos.⁴² However, technical advances in freezing and thawing oocytes are evolving.²⁰

Cryopreservation of ovarian tissue does not involve stimulation of the ovaries (and hence high levels of circulating estrogen), but is still experimental and should be done only at reproductive research centers under monitoring by the Institutional Review Boards of participating institutions.⁴⁴ Ovarian tissue is harvested, usually laparoscopically, and cryopreserved (frozen) for later use. Tissue can be transplanted with the hope of regaining ovarian function. Successful re-implantation and harvesting of mature oocytes have been achieved,¹⁷ and a total of 12 live births from cryopreserved ovarian tissue have been reported in the literature.⁴⁵ In the future, as advances occur in the field, mature eggs ready for transplantation or implantation may be coaxed from the immature eggs in a woman's frozen ovarian tissue. These approaches are highly experimental and women should understand this when considering cryopreservation. However, this procedure does not require weeks of hormonal stimulation and can be done immediately, both aspects that may be attractive to women who wish to prevent substantial delay in cancer treatment.

Some small studies have suggested that women whose ovarian function was suppressed during chemotherapy were less likely to experience ovarian failure,^{46–48} but others have not.⁴⁹ GnRH agonists and antagonists are used to achieve ovarian suppression, but this also puts a woman in chemical menopause. Prospective randomized trials of sufficient power have not been performed to determine whether ovarian suppression is protective, and this cannot be solely relied upon to preserve ovarian function.^{17, 50} A large randomized controlled trial is on-going to address the role of ovarian suppression in protecting fertility.

Finally, women may choose their chemotherapy regimen based on its impact on ovarian function. For instance, in breast cancer treatment, four cycles of AC therapy (Adriamycin and Cyclophosphamide) result in very low rates of amenorrhea (10–15%) as compared to six cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) therapy (20–60%),^{51–53} with no difference in survival. Choice of treatment for ovarian⁵⁴ and hematologic cancers³³ can also be tailored to reduce the risk of infertility, with equivalent clinical responses. Women may decide to forgo chemotherapy entirely if the absolute gains in survival are small. Although the number of young women who alter their treatment based on fertility concerns is not known, Partridge *et al*¹³ found that fertility concerns affected treatment choices in 28% of their web-based sample of young breast cancer survivors.

Protecting the ovaries from pelvic radiation can be attempted by oophoropexy. Oophoropexy is a surgical procedure that moves the ovaries out of the field of pelvic radiation. It can be done laparoscopically just before radiation is initiated, or by laparotomy at the time of primary treatment for cancer. The effectiveness of the procedure varies greatly, and estimates of efficacy range from 16–90%.^{23, 55} Even when ovarian function is preserved, IVF may be required to restore fertility because of the position of the ovaries. In addition, oophoropexy does not protect the ovaries from whole body or spine radiation, chemotherapy, or injury to the vasculature during the surgery itself.

PREGNANCY OUTCOMES IN CANCER SURVIVORS

Rates of pregnancy among cancer survivors are generally lower than age-matched peers.⁵⁶ This may reflect both higher rates of infertility, as well as reduced attempts at conception. Pregnancy does not appear to increase the risk of cancer recurrence.⁵⁷ However, there has been considerable concern and debate regarding the safety of pregnancy in women with hormone-sensitive tumors. The high levels of circulating sex hormones could theoretically increase the chances of recurrence. Studies among breast cancer survivors do not suggest an increased risk of recurrence with pregnancy.^{58–60} In fact several suggest a decreased risk of recurrence,^{58, 59} but there are methodological problems with these studies including selection bias (only healthy women with the best prognosis pursue pregnancy) and publication bias (studies are unpublished because they are small studies or case series).

Cancer patients also report concerns regarding the risks of chemotherapy to their offspring and the safety of pregnancy itself.^{61, 62} Chemotherapy does not appear to increase the risk of abnormalities in offspring, as long as pregnancy is delayed at least 6 months following treatment.^{60, 63} However, Tamoxifen, used as adjuvant chemotherapy in premenopausal women with ER+ breast cancer tumors to prevent recurrence, does increase the risk of fetal abnormalities and pregnancy is contraindicated while on therapy.^{60, 64} There is no evidence that a history of cancer increases cancer risk in offspring, a concern many cancer survivors have regarding their offspring.⁶⁵ An exception is individuals who harbor autosomal dominant genetic mutations such as BRCA-1 or BRCA-2, whose offspring have a 50% chance of inheriting the gene. Radiation to the pelvis does increase the risk of premature delivery and birth weight is lower in women who have received pelvic radiation.⁶⁵ A pregnancy in a woman who has received pelvic radiation should be considered a high-risk pregnancy.

For women who cannot become pregnant naturally, IVF can be attempted. IVF after cancer treatment is an unusual occurrence and experience is extremely limited. However, one case series by Ginsburg *et al*⁶⁶ suggested women with early breast cancer can be stimulated successfully, though the number of oocytes and embryos retrieved is lower. Several researchers^{59, 60, 63} have called for national registries to help quantify and study these issues in female cancer survivors.

THE PSYCHOSOCIAL IMPACT OF FERTILITY IN CANCER SURVIVORS

Infertility alone is associated with significant psychological distress with levels of depression twice that of the normal population, and quality of life is reduced in areas of emotional well-being, relationships and sexuality.^{67, 68} When infertility is superimposed on cancer, there can be great stress on the patient, partner and family.⁶⁹ Even for persons who may have not planned to have children, the threat of infertility can result in a deep sense of loss and anger.

Women diagnosed with cancer must process complex information regarding cancer treatment options. The process of diagnosis and treatment decision-making has long been recognized as a particularly difficult and challenging time for women. Fertility preservation options are also very complex, requiring women to weigh their desire for preserving childbearing potential

against the possible treatment delays and uncertain risks of fertility preservation options. Given that physicians often do not discuss these issues with their cancer patients, women may perceive physician failure to raise the issue as an implicit dismissal of its importance or feasibility. Some women may feel that they should be grateful just to survive their cancer.

However, we know that issues related to fertility remain very important to women in the short^{13, 62} and long-term.⁷⁰ The loss of fertility is sometimes felt as painfully as the cancer diagnosis itself.^{63, 71} In qualitative studies that have inquired as to the motivations for having children after cancer among breast cancer survivors, women cite a sense of reclaiming their lives, a wish to feel normal again, and a desire to achieve the goals they set prior to their cancer diagnosis.^{71, 72} Surveys of breast cancer survivors have found that infertility is an important long-term survivorship issue which has a negative impact on women's quality of life.^{7, 73}

Schover *et al*⁶¹ surveyed a sample of 100 young female cancer survivors age 14 and older who were free of disease, specifically addressing issues of fertility. The average age of young women in the sample was 26 and the mean time since diagnosis was 5 years. They found that the experience of cancer did not decrease the desire to have children, and in fact it actually increased the value placed on parenthood and family ties. Of those childless at the time of the questionnaire, 76% wanted children in the future, and over 30% of those who already had children at diagnosis wanted additional children.

Zanagnolo *et al*⁷⁴ examined attitudes of 75 women who underwent conservative treatment for ovarian cancer and found that cancer did not diminish their desire to have children in 78% of women, and over half of women were concerned about the effects of removing one ovary on infertility risk. The authors also found that infertility concerns were associated with increased distress in these women, regardless of whether they already had children. A review of the psycho-social outcomes in women with gestational trophoblastic disease found that women had persistent fears regarding their ability to carry a normal pregnancy to term and also worried about pregnancy increasing the risk of disease recurrence.⁷⁵ Women who had children before their diagnosis, and women who bore children after their diagnosis had the highest quality of life scores.

In a cross-sectional study of 231 women diagnosed between ages 17–45 with cervical cancer, gestational trophoblastic tumors, or lymphoma, Wenzel *et al*⁷⁶ found that greater reproductive concerns were associated with significantly lower quality of life and increased cancer-specific distress. Women unable to conceive after cancer treatment reported significantly more reproductive concerns, poorer mental health, and lower psychological well-being than women who were able to have children. Cervical cancer survivors reported the most reproductive concerns. Carter *et al*⁶⁷ examined quality of life measures in 20 women aged 29–49 with known infertility due to gynecologic cancer treatment, and found 40% met the clinical criteria for depression on the CES-D. Approximately half of the women experienced trouble accepting infertility, yearning to give birth, or anger over their infertility.

Regardless of the type of cancer women face, the limited research conducted to date indicates that fertility concerns are prevalent, and negatively impact on a woman's quality of life. The consistency of these findings points to the importance of discussing fertility issues with premenopausal women in the clinical setting prior to the initiation of cancer treatment. Fertility changes and options to preserve fertility must be discussed *before* treatment is begun, when options to prevent fertility loss are still feasible. However, there are a number of potential barriers to discussing fertility issues.

BARRIERS TO DISCUSSING FERTILITY OUTCOMES

Research regarding oncologists' discussions with premenopausal women regarding fertility changes associated with breast cancer treatment suggests that between one-third to two-thirds of women are not counseled regarding the impact of cancer treatment on their fertility.^{13, 77} Rates for other cancers are even lower.⁷⁸ Qualitative studies have indicated that women want information both about the risks of becoming infertile, as well as options for protecting or preserving their fertility.¹⁰ Yet even when counseled, the information received is often not adequate from the patient's perspective.^{13, 62, 79}

Limited research has examined the barriers and facilitators of fertility discussions from a medical provider's perspective.^{80–82} These studies suggest that awareness and comfort in discussing fertility issues, as well as knowledge of available resources, play a role in either facilitating discussions or hindering the discussion of fertility. In addition, providers rated the importance of fertility to their patients as low, in contrast to patients, who rate fertility issues as quite important.⁸¹ Often, providers do not raise fertility issues unless the patient herself raises them.⁸²

Time constraints are also an often-cited barrier to fertility discussions. In the US there is increasing pressure to see more and more patients within defined periods of time to offset decreasing reimbursement and increasing administrative costs. In the context of visits prior to cancer treatment, providers are challenged to discuss the many cancer treatment options available to women, with their associated risks and benefits. To many providers, adding a discussion of potential threats to fertility associated with treatment, as well as fertility preservation options, may seem overwhelming. The use of oncology nurses and social workers to provide much of the counseling regarding fertility and cancer has been proposed as a solution to this issue.⁸³ Resources such as Fertile Hope, Susan G. Komen Foundation, and Lance Armstrong Foundation all provide information in web and print form that can assist women with cancer and their providers in discussing fertility issues.

Characteristics of the cancer, such as advanced stage, may also impact whether fertility issues are discussed. Providers may neglect to discuss fertility issues in women with a poor prognosis. However, it is impossible to know which women will survive and which women will not---even among women diagnosed with advanced stage cancer, some women will live. In addition, personal characteristics such as financial status, marital status, or age may also present barriers to oncologists' raising fertility issues with premenopausal women. However, findings from a study of young breast cancer survivors indicated that these characteristics were not associated with interest in fertility information.¹³ Only the desire for children at time of diagnosis, number of previous pregnancies and previous infertility were associated with concern regarding infertility. The safest and most equitable approach is to raise fertility issues with every patient.

Fertility issues in premenopausal women diagnosed with cancer present important challenges to the provider and to the patient. However, failure to discuss these options adequately can have lasting negative consequences on a woman's quality of life. Physician education interventions should seek to improve the knowledge of fertility preservation options, and of locally and nationally available resources. In addition, incorporating fertility issues into oncology training programs would both improve comfort and knowledge, and would be an important signal of the importance of the topic.

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Table 1

Risk of amenorrhea with treatments in common cancers among premenopausal women

Breast Cancer	Therapy	Age	Risk
	AC	<40	low
		40+	intermediate
	CMF	<30	low
		30–39	intermediate
		40+	high
	CEF	<30	low
		30–39	intermediate
		40+	high
	CAF	<30	low
		30–39	intermediate
		40+	high
	Trastuzumab	All ages	unknown
	Taxanes	All ages	unknown
Hematologic malignancies			
General therapies	BMT	All ages	high
	Whole body irradiation, spinal radiation, pelvic radiation	All ages	high
Lymphomas			
Hodgkin's	ABVD	All ages	low
	Protocols with procarbazine (MOPP, BEACOPP)	All ages	high
Non-Hodgkin's Lymphoma	ABVD, CHOP	All ages	low
	Cyclophosphamide 7.5 g/m ²	All ages	high
Leukemias			
AML- Acute Myeloid Leukemia	Anthracycline, cytarabine	All ages	low
ALL-Acute lymphoblastic leukemia	Cyclophosphamide 7.5 g/m ²	All ages	high
Colorectal	Irotectan, cetuximab, bevacizumab	All ages	unknown
	Alkylating agents	All ages	High
	Pelvic radiation (Rectal CA)	All ages	High
Ovarian	Alkylating agents plus radiation	All ages	High risk

Adapted from Lee et al 2006 & Maltaris et al 2006

High Risk >80%, Intermediate 20–80%, Low <20%

BMT = Bone Marrow Transplant

AC= adriamycin, cyclophosphamide

CMF= cyclophosphamide, methotrexate, fluorouracil

CEF= cyclophosphamide, epirubicin, fluorouracil

CAF=Cyclophosphamide, adriamycin, fluorouracil

ABVD=adriamycin, bleomycin, vinblastine, dacarbazine

CHOP=cyclophosphamide, adriamycin, vincristine, prednisone

MOPP= Mechlorethamine, Vincristine, Prednisone, Procarbazine

BEACOPP= cyclophosphamide, adriamycin, etoposide, vincristine, bleomycin, procarbazine, prednisone

Table 2

Fertility Preservation Options

	In-Vitro Fertilization Options ^{1,2}			Ovarian Cryo-preservation	Ovarian Suppression	Radical trachelectomy	Oophoropexy
	Embryo Freezing	Egg Freezing	Donor Embryos/eggs				
What is it?	IVF cycle – creating embryo from egg and sperm and freezing them for later implantation into patient or into a gestational carrier ³	Harvesting eggs, which are later used to create embryos for implantation into patient or a gestational carrier	Embryos or egg donated, patient could then carry the pregnancy. Other option would be to obtain a surrogate, whereby another woman would both provide egg <i>and</i> carry the pregnancy	Freezing ovarian tissue & reimplantation after treatment	Shutting down of ovaries using GnRH analogues or antagonists	Modified cervical cancer surgery to preserve the uterus	Moving ovaries out of field of pelvic radiation
When?	Best results before treatment	Best results before treatment	After treatment	Best results before treatment	During treatment	Must be performed as part of cancer treatment	Before radiation
Time and effort required	3–6 wks for IVF, which includes daily hormonal injections, frequent blood draws, multiple vaginal ultrasounds, and outpatient surgical procedure.		None before cancer treatment, but requires finding a suitable donor, and then undergoing IVF.	Outpatient surgical procedure to obtain ovarian tissue; possible 2 nd procedure to reimplant tissue	Appointment for monthly injections	Surgery recovery similar to traditional radical hysterectomy with LN dissection	Laparoscopic surgery
Risks	-Potential delay of cancer treatment - -Hyperstimulation syndrome ⁴ -Risks of anesthesia and infection -Unclear risks of IVF on cancer recurrence -Pregnancy could theoretically increase risk of hormone-sensitive cancers, although observational data suggest safe		-Risks of anesthesia and infection -Unclear risks of IVF on cancer recurrence -Pregnancy could theoretically increase risk of hormone-sensitive cancers, although observational data suggest safe	-Risks of anesthesia and infection	Symptoms of menopause such as night sweats, sleep and mood disturbances	-Surgical risks similar to traditional cervical cancer surgery. -Limited data suggest risk of recurrence similar as well	-Risks of anesthesia and infection -May require IVF to become pregnant -Surgery can cause disruptions in ovarian blood supply which can damage ovaries, cyst formation
Success rates	~40% per transfer; varies by age & center	~ one quarter that of traditional IVF	Slightly higher than embryo freezing	-12 live births reported worldwide -experimental	Unknown: conflicting results reported -experimental	~70% who <i>try</i> to conceive are successful, but only small percentage of women attempt	~60–90% will resume menses (range 16–90%)
Misc	Need partner or donor sperm -May be	Do not need sperm at time of harvesting	Can use partner sperm May be religious objections	Advanced breast cancer, some lymphomas not	Puts you into chemical menopause (reversible)	Increased risk of premature labor and 2 nd trimester loss	Does nothing to protect from chemotherapy, which is often

	In-Vitro Fertilization Options ^{1,2}			Ovarian Cryo-preservation	Ovarian Suppression	Radical trachelectomy	Oophoropexy
	Embryo Freezing	Egg Freezing	Donor Embryos/eggs				
	religious objections		-If choose surrogacy (other woman carries child), laws in each state differ	suitable due to concern for ovarian mets		-requires surgeon is trained in technique, may require travel	part of cancer treatment regimen

¹ IVF = In-Vitro Fertilization – process of stimulating ovaries to produce many eggs, then extracting them surgically and creating embryos

² Woman can choose to carry pregnancy herself, or use a surrogate (a woman who carries a baby for another couple or individual) for any of the IVF options.

³ Gestational Carrier – A woman carries a child that is genetically not related to her (implanted embryo) for another person/couple

⁴ Hyperstimulation syndrome occurs when the ovaries produce excessive mature egg follicles and results in abdominal pain, bloating, aborted IVF cycle and extremely rarely surgical intervention to relieve the condition