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Creating a Continuum of Care: Integrating Obstetricians and Gynecologists in the Care of Young Cancer Patients

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Abstract: Cancer therapy can be lifesaving but significantly diminish female reproductive potential. This review provides an overview of the deleterious effects of cancer treatments on reproductive function, the fertility preservation options currently available for young women, and the outcomes of pregnancy after cancer treatment. In addition, special considerations for women who are diagnosed with cancer during pregnancy are discussed. To optimize the continuum of care for the patient, new corridors of communication between obstetricians, gynecologists, and oncology specialists must be developed to ensure the best outcomes for the patient, both in terms of cancer treatment and fertility preservation.

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Introduction: The Need for Oncofertility Present and Future

Some 90,000 children and young adults below the age of 40 years are diagnosed with cancer each year in the United States.[1] The success of modern cancer therapy regimens has improved the 5-year relative survival rate to over 80% for these individuals,[1] and now more than ever, survivors of childhood and young adult cancers have the opportunity to consider quality of life issues. For a large number of patients in their reproductive age, a major priority after surviving the disease

is to protect fertility from the gonadotoxic effects of chemotherapy or ionizing radiation. Cancer treatment may threaten fertility and negatively impact subsequent reproductive function in both males and females. For males, sperm cryopreservation before cancer treatment is a noninvasive and well-established method for preserving fertility. Fertility preservation for females presents multiple challenges, both because of the scarcity of the female gamete as well as difficulties in obtaining and storing the tissue. Further, utilization of stored female gametes to achieve a successful pregnancy in the future presents its own set of biological concerns and complications.

This review focuses primarily on the young female population before and during the reproductive years, and aims to provide obstetricians and gynecologists with a comprehensive overview of how cancer treatment can threaten fertility and adversely affect pregnancy outcomes, what fertility preservation options are available, and the considerations for achieving a healthy pregnancy in cancer survivors. In addition, a discussion of fertility management in the unique and complex situation of a patient diagnosed with cancer during pregnancy will follow. As the number of cancer survivors continues to increase, it will be of critical importance to create a continuum of care between obstetricians, gynecologists, and oncology specialists.

There exists an urgent need to provide young people in the face of a cancer diagnosis with the most pertinent information to make informed decisions about their future fertility. The field of oncofertility was initiated in 2006 to consolidate resources focused on preserving and restoring reproductive function in patients diagnosed with cancer into an integrated network. The interdisciplinary approach integrates clinicians, basic science researchers, social scientists, and ethicists so that research breakthroughs can be translated efficiently and safely to clinical applications.[2] National organizations such as the American Society of Clinical Oncology and American Society of Reproductive Medicine support the mission of oncofertility and have issued recommendations for clinicians on discussing the potential for infertility with cancer treatment and the possibilities for fertility preservation.[3,4]

Women diagnosed with cancer during pregnancy comprise a special niche of patients currently with an unmet and urgent need for oncofertility. Management of this cohort of patients is especially complex because of their current gestation, and requires a multidisciplinary team of specialists to oversee optimal care for mother, fetus, and future fertility. The expansion of the oncofertility field into such complex areas will allow further development of the discipline as an authoritative voice in fertility preservation. The continued growth and success of oncofertility requires that clinicians, including obstetricians and gynecologists, provide their patients with the appropriate knowledge, counseling, and referrals necessary to achieve optimal fertility and pregnancy outcomes at all phases of cancer treatment.

Impact of Cancer Treatment on Reproductive Health

Cancer treatment in premenopausal women can alter reproductive capacity and gynecologic health. Although therapeutic regimens involving surgery, chemotherapy, and radiation are improving cancer survival rates, sequelae of cancer treatment are becoming increasingly important. In order to achieve an autonomous pregnancy and carry a fetus, a woman requires a functioning hypothalamic-pituitary-ovarian axis and a receptive uterus. Importantly, cancer therapy can affect each of these anatomic and

physiological parameters. The pathophysiology of gonadotoxic chemotherapy and radiation will be reviewed here to better facilitate the obstetrician and gynecologists' ability to counsel their patients on the reproductive outcomes of cancer therapy.

The ovarian reserve is comprised of a nonrenewable, finite pool of primordial follicles and represents a woman's reproductive longevity. Systemic chemotherapy is often used in treating solid tumors, hematological malignancies, and in conditioning regimens for bone marrow transplants. Although oncologists rely on systemic agents as important treatment tools, a common side-effect is infertility. Chemotherapy-induced ovarian damage can hasten follicular depletion leading to primary ovarian insufficiency (POI). POI encompasses an array of ovarian dysfunction, both transient and permanent. Clinically, POI is defined as amenorrhea, sex steroid deficiency, and serum follicle-stimulating hormone levels >40 IU/L in women below 40 years of age.[5] Moreover, the consequences of POI include significant systemic sequelae including cardiovascular, musculoskeletal, and psychosocial disease.

There are 6 main classes of chemotherapeutic agents based on mechanism of action: alkylating agents, antimitotics, antibiotics, antimetabolites, plant alkaloids, and the taxanes (Table 1—gonadotoxicity of specific agents). Of all chemotherapeutic agents, alkylating agents carry the highest risk of infertility.[6] The most commonly used agent in this class, cyclophosphamide, is associated with DNA crosslinking in granulosa cells leading to decreased circulating levels of estrogen and progesterone. Although fertility loss is an important side effect of systemic treatment, investigators are only beginning to delineate the mechanism of chemotherapy-induced ovarian failure. Ultrastructurally, it has been shown that chemotherapy-induced ovarian insufficiency is associated with ovarian fibrosis. Namely, this process mimics the normal ovarian aging process with collagen fibers replacing ovarian stromal cells. The immediate toxicity of chemotherapeutics on growing granulosa cells leads to a significant decrease in anti-Mullerian hormone levels.[7] In fact, serum anti-Mullerian hormone levels have proven to be a more reliable marker of fertility than menstruation and can be used clinically to assess ovarian reserve.[8] In addition, evidence has shown that apoptosis is the primary mechanism responsible for primordial follicle loss.[9,10] As more basic research is conducted in both animal models and clinical trials to understand the mechanism of chemotherapy-induced follicular loss, treatment plans and novel therapies can be individualized to optimally treat the malignancy and preserve future fertility.

The impact of radiation on the body is largely dependent on the dose, duration, and frequency of exposure, as well as the age at time of treatment. At the cellular level, the toxicity of ionizing radiation primarily results in damage to DNA and the nucleus, and thus has the potential to affect a wide range of organs.[11] Because actively dividing cells are more sensitive to radiation than nondividing cells, the quiescent state of primordial follicles provides some protection against the effects of ionizing radiation compared with growing follicles. However, it is estimated that the LD_{50} of the human oocyte, defined as the radiation dose required to destroy 50% of primordial follicles, is <2 Gy.[12] Ovarian failure has been reported in 97% of childhood cancer survivors after abdominal irradiation totaling 20 to 30 Gy,[13] and in 90% of adult cancer survivors. Using mathematical modeling, it is now possible to predict the age of ovarian failure and the estimated sterilizing dose after radiotherapy at any given age.[14] This data will be essential when evaluating and counseling a patient about the need for fertility preservation.

TABLE 1. Gonadotoxicities of Chemotherapeutic Agents

Category	Agents	Gonadotoxicity
Alkylating agents	Nitrogen mustards: cyclophosphamide, ifosfamide, chlorambucil, chlormethine, mechlorethamine, melphalan, bendamustine, trofofamide, uramustine Nitrosureas: carmustine, foternustine, lomustine, nimustine, prednimustine, ranimustine, semustine, streptozocin Platinum analogs (alkylating-like): carboplatin, cisplatin, nedaplatin, oxaliplatin, triplatin tetranitrate, satraplatin Alkyl sulfonates: busulfan, mannosulfan, treosulfan Hydrazines: procarbazine Triazenes: dacarbazine and temozolomide Aziridines: carboquone, thio TEPA, triaziquone, teithylenemelamine	High
Antimitotics	Taxanes: docetaxel, larotaxel, ortataxel, paclitaxel, tesetaxel Vinca alkyloids: vinblastine, vincristine, vinflunine, vindesine, vinorelbine	Moderate
Antibiotics	Anthracyclines: aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, amrubicin, pirarubicin, mitoxantrone, pixantrone, valrubicin, zorubicin Streptomyces: actinomycin, bleomycin, mitomycin, picamycin, hydrourea	Mild to moderate
Antimetabolites	Folic acid: aminopterin, methotrexate, pemetrexed, raltitrexed Purine: cladribine, clofarabine, fludarabine, mercaptopurine, pentostatin, thioguanine Pyrimidine: cytarabine, decitabine, fluorouracil, floxuridine, gemcitabine, enocitabine, sapacitabine, capecitabine	Mild
Topoisomerase inhibitors	Camptotheca: camptothecin, topotecan, irinotecan, rubitecan, belotecan Podophyllum: etoposide and teniposide	Unknown
Monoclonal antibodies	Cetuximab, panitumumab, traxtuzumab, ritutumomab, bevacizumab	Unknown
Tyrosine kinase inhibitors	Axitinib, bosutinib, cediranib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, semaxanib, sorafenib, sunitinib, vandetanib	Unknown

The uterus is the site of embryonic implantation and functions primarily to support growth and development of the fetus. Uterine function may be impaired after radiation doses of 14 to 30 Gy as a consequence of volume reduction, disruption of the uterine vasculature, and impairment of musculature elasticity.[15] In addition, the remodeling of uterine size and shape that normally occurs during puberty may be limited as a result of ovarian radiation toxicity.[16] Owing to these effects on the uterus, radiation exposure can negatively impact the ability of a woman to maintain a healthy pregnancy even if conception occurs.

Finally, the neuroendocrine axis that controls the release of reproductive hormones, and regulates the menstrual cycle and pregnancy, may also be impacted by radiation therapy. In particular, adults and children treated with cranial radiation for the management of brain neoplasms may have deficits in hypothalamic and pituitary function.[17] In children treated for acute lymphoblastic leukemia, higher doses (> 24 Gy) have been associated with delayed puberty, and lower doses (< 24 Gy) associated with precocious puberty.[18]

Assessing patients' risk of treatment-induced ovarian failure and pregnancy

complications is difficult because of the many variables of treatment regimens, patient gynecologic history, and cancer diagnosis. Thus, clinicians must integrate several factors to best assess the impact of cancer treatment on a woman's reproductive health and lifespan, including her age, the agents used, and the cumulative dose.

Fertility Preservation in Patients With Cancer

Owing to the gonadotoxicity of chemotherapy regimens and ionizing radiation, it is necessary to evaluate a woman's risk for diminished or lost fertility before the initiation of such therapies. If high risk of ovarian failure is expected, fertility preservation options should be discussed. Current research in the laboratory holds much promise for fertility preservation, and oncofertility is emerging as an essential field in the management of newly diagnosed young cancer patients. Although fertility preservation options range from mature technologies to experimental protocols, determining the best course of treatment depends primarily on the patient's age, diagnosis, and cancer treatment.[19] This section will review the standard and investigational fertility preservation options available to a woman in the face of a new cancer diagnosis, with a particular focus on the most viable options currently: embryo, egg, and ovarian tissue cryopreservation. Table 2 summarizes the options for fertility preservation in females.

Embryo cryopreservation is the most mature and successful technology, and should be the first-line choice for fertility management whenever practical. The American Society of Reproductive Medicine maintains that embryo cryopreservation is the only established method for fertility preservation in women; all other methods are experimental and should only be offered in a research setting with Institutional Review Board approval.[4] This approach typically requires ovarian hyperstimulation with daily gonadotropin injections for approximately 2 weeks. When mature, eggs are collected from the ovaries by ultrasound-guided transvaginal needle aspiration of follicles followed by in vitro fertilization (IVF) and cryopreservation.[20] After cancer treatment, embryos can be thawed and transferred back to the uterus of the patient. IVF is a well-established technology that accounts for over 3 million live births since the first report about 30 years ago. Embryo survival after freezing and thawing is excellent, and cumulative pregnancy rates average around 40%.[21]

Despite its overall success, embryo cryopreservation raises several concerns. First, because hormonal stimulation is initiated from the onset of menses, a delay of 2 to 6 weeks is necessary before the initiation of cancer treatment. Second, embryo cryopreservation requires hormonal stimulation, which is not an option for prepubertal girls and contraindicated in women with hormone-sensitive cancers.[20] Although egg collection can be performed without ovarian stimulation (natural cycle-IVF), the embryo yield is lower with this technique. Third, a partner or sperm donor is required for the creation of embryos and is not feasible for all patients. Finally, ethical, religious, and legal issues are associated with the creation and usage of embryos.[22]

Egg cryopreservation is a technique that may be particularly attractive to women who do not wish to create embryos for personal, ethical, or religious reasons. Similar to embryo cryopreservation, freezing of eggs requires ovarian stimulation and aspiration of mature eggs, and thus similar concerns regarding treatment delay and hyperstimulation exist. Advances in the freezing and thawing processes for unfertilized eggs has improved egg survival with fertilization rates comparable with those of eggs used in standard IVF procedures.[23] One study

TABLE 2. Fertility Preservation and Pregnancy Options in Women

Fertility Option	S/I	Interventions Precancer Treatment	Interventions Postcancer Treatment (for Pregnancy)	Advantages	Disadvantages*
Methods to Protect Female Gametes Outside the Body					
Embryo cryopreservation	S	Ovarian stimulation Aspiration of mature eggs IVF Freezing of embryos	Embryo transfer	Most established method for fertility preservation in women	Requires hyperstimulation Delays cancer treatment 2-6 wk Requires sperm donor Generates embryos
Egg cryopreservation	I	Ovarian stimulation Aspiration of mature eggs Freezing of eggs	IVF Embryo transfer	Maintains reproductive autonomy Becoming viable reproductive technology	Requires hyperstimulation Delays cancer treatment 2-6 wk
Oocyte cryopreservation	I	Ovarian stimulation Aspiration of immature oocytes Freezing of oocytes	IVM IVF Embryo transfer		Requires hyperstimulation Delays cancer treatment 2-6 wk Less effective than egg cryo
Natural cycle egg or oocyte cryopreservation	I	Aspiration of oocytes and/or eggs Freezing of oocytes and/or eggs	IVF, embryo transfer (for eggs) IVM, IVF, and embryo transfer (for oocytes)	Does not require hyperstimulation	Gamete yield very low
Ovarian tissue cryopreservation	I	Surgery to remove ovarian tissue Freezing of ovarian cortical strips	Quilting of ovarian cortical strips Autotransplantation of ovarian tissue May require IVF Isolation of immature follicles, IVIG, IVM, IVF, embryo transfer	Can be performed at any stage of menstrual cycle Avoids risk of reintroducing cancerous cells	Has potential to reintroduce cancerous cells Transplant has limited lifespan No trials in humans to date
Isolation of oocytes from an ovarian biopsy	I	Immature oocyte collection Freezing of immature oocytes	IVM IVF Embryo transfer	Can be performed at any stage of the menstrual cycle	
Methods to Protect Female Gametes Inside the Body					
Gonadal shielding	S	Reproductive organs shielded from radiation	None		Does not prevent natural ovarian aging Only possible with certain radiation fields

TABLE 2. (continued)

Oophoropexy	S	Surgery to move ovaries away from radiation field	Surgery for ovarian repositioning may or may not be necessary May require IVF		Does not prevent natural ovarian aging Does not protect the uterus Risks for ovarian dysfunction
Ovarian suppression antagonists	I	GnRH analogs or antagonists given to suppress growth and development of follicles	None	Noninvasive	Controversial efficacy
Third Party/Nonbiological Fetility Options					
Egg/embryo donor		None	Obtain donor eggs or embryos Embryo transfer to patient or surrogate		
Surrogate		Collection and cryopreservation of embryo, egg, or oocyte specimens as described above	Patient embryos thawed and transferred to surrogate Patient oocytes or eggs thawed for IVF or IVM/IVF, embryo transfer to surrogate	Avoids pregnancy complications of uterine dysfunction due to cancer treatment	
Adoption		None	Adopt nonbiological child	Does not rely on patient's fertility	

* In addition to the disadvantages listed, global concerns such as cost and availability exist for all fertility preservation options. GnRH indicates gonadotropin-releasing hormone; I, investigational; IVF, in vitro fertilization; IVIG, in vitro follicle growth; IVM, in vitro maturation; S, standard.

published in 2009 tabulated over 900 live births worldwide from cryopreserved mature eggs. In addition, the authors found no differences in the risk of congenital anomalies when compared with naturally conceived infants.[23] Data on egg cryopreservation is promising and the technology will likely attain more prominence in the future, but because of its relative infancy, women choosing between egg and embryo cryopreservation are counseled toward the latter, even if it requires purchasing donor sperm. A possible compromise may be to divide her retrieved eggs such that a fraction is cryopreserved as eggs, and the other fraction is fertilized to create embryos for storage.

Ovarian tissue cryopreservation is a viable option for women who do not have sufficient time before starting cancer therapy or who cannot be exposed to ovarian stimulation, including prepubertal girls and females diagnosed with hormone-responsive cancers. In this technique, all or a portion of one or both ovaries are removed followed by dissection of the ovarian cortex into thin strips for cryopreservation. Several options exist for managing the ovarian tissue: ovarian tissue cryopreservation followed by

autotransplantation or in vitro follicle growth, or immature oocyte isolation. Although all are investigational, thawing and orthotopic transplantation of cryopreserved ovarian tissue back to the patient after cancer treatment has been successful in restoring hormonal function and resulted in 13 live births worldwide, both by natural conception and IVF techniques.[24] Nevertheless, the ovarian tissue may harbor malignant cells, and transplantation carries the inherent risk of cancer reintroduction.

A theoretical option that addresses this risk is the isolation of individual follicles from the cryopreserved cortical tissue for in vitro follicle growth, egg maturation, fertilization, and ultimately embryo transfer. Although this technique has resulted in the birth of healthy mouse pups in a murine model,[25] the technology is still experimental and will have a great deal of further investigation before a trial in humans. Finally, immature oocytes can be isolated from ovarian tissue or a natural cycle and cryopreserved, or matured in vitro before storage. It is important to note, however, that success rates for a viable pregnancy will decrease with every step completed "in vitro," and thus techniques that require the removal of the female gamete at earlier stages will likely result in decreased fertilization and implantation rates.

If pelvic radiation is needed, the ovaries can be surgically transposed as far as possible from the planned radiation field. This procedure, known as oophoropexy, can be performed at the time of abdominal surgery related to the primary tumor, or in a separate procedure, often involving minimally invasive surgery. Several small case reports of patients diagnosed with Hodgkin lymphoma or rectal cancer who used oophorpexy show some success of this technique in maintaining normal ovarian function and achieving a healthy pregnancy.[26,27]

Although techniques such as oophoropexy and gonadal shielding provide some protection to the ovaries against the damaging effects of ionizing radiation, these techniques do not protect the uterus. Thus, regardless of whether embryos, eggs, or ovarian tissue are cryopreserved, a patient with limited uterine function or who has had a hysterectomy will require the use of a gestational carrier to achieve a successful pregnancy. Similarly, patients who did not have the opportunity for fertility preservation before cancer treatment may have reduced ovarian and uterine function. In these circumstances, and for those who have selected storage of their own gametes before cancer treatment, the patient should be counseled on nonbiological or third-party options, such as surrogacy, use of donor egg or embryos, and adoption.

For a young woman facing a cancer diagnosis along with its short-term and long-term sequelae, the patient-physician discussions necessary are extensive and overwhelming. Owing to the complexities of the medical decision-making process reflected in these situations, referral to an established institution with expertise and written protocols for fertility preservation is highly recommended. Further, using an interdisciplinary team of physicians, including an oncologist and reproductive endocrinologist at the core will provide the best care for the patient regarding the most appropriate cancer treatment and fertility preservation options. It is important that realistic expectations be discussed, both in terms of the patient's cancer prognosis and success rate of any fertility preservation option attempted. If biological tissue is stored, documenting the patient's wishes in the event of death or divorce will help to avoid potential legal pitfalls regarding tissue ownership and use.

Pregnancy After Cancer

Although gamete removal and preservation before cancer treatment affords a

woman the opportunity to consider her fertility options after cancer treatment and remission, many concerns regarding the actual pregnancy may arise when she is ready to conceive and should be addressed appropriately. Specifically, cancer survivors may fear pregnancy because of concerns regarding cancer recurrence, and potential detrimental outcomes for maternal or fetal health during the pregnancy. The literature provides some reassurance regarding these issues, which will be discussed in regards to the risks and outcomes for pregnancy in cancer survivors.

Multiple studies to date suggest no adverse outcomes of pregnancy on cancer recurrence or survival, even for hormone-responsive malignancies such as breast cancer. For example, 1 large population-based study that analyzed 465 pregnancies in 371 breast cancer patients posttreatment noted that a full-term pregnancy was associated with a reduced risk of breast cancer mortality compared with other breast cancer survivors.[28] Miscarriages and induced abortions did not negatively impact survival. The authors concluded that there was no evidence to suggest adverse influences on prognosis due to pregnancy after breast cancer.

Many cancer survivors question the optimal interval between completion of chemotherapy and attempting conception. Most oncologists recommend waiting 2 to 5 years, the time frame when most relapses occur. However, this recommendation is largely anecdotal and there is no solid evidence to suggest that postponing conception will alter the outcome of the cancer or pregnancy. Data from 1 recent retrospective study examining 123 women who were diagnosed with breast cancer and subsequently conceived suggests that for women with localized disease and a good prognosis, conception at 6 months after treatment is unlikely to increase mortality, although the general recommendation to wait 2 years may still be valid for those who are receiving treatment or have systemic disease.[29] As it takes about 6 months for a new cohort of follicles to be recruited for growth and maturation, this timeframe is recommended to allow any eggs damaged by chemotherapy or radiation to be eliminated.

On account of the long-term toxicities associated with chemotherapy and radiation, damage to the heart, lungs, and uterus can compromise a patient's health and ability to carry a pregnancy. One study found evidence that pregnancy may exacerbate the cardiac toxicity caused by doxorubicin in women treated for childhood cancers by further reducing the ejection fraction.[30] Other pregnancy complications, such as miscarriage, low birth weight, and premature delivery are largely associated with the adverse effect of pelvic radiation on uterine growth and blood flow. A study published by Signorello et al[31] in 2010 found that uterine and ovarian irradiation significantly increased the risk of stillbirth or neonatal death among childhood cancer survivors.

A final concern among cancer survivors considering pregnancy is the risk of birth defects and the risk of passing their cancer onto their offspring. Outside the pool of genetically linked cancers, which comprises only 5% to 10% of all cancers,[32] there is scant evidence that a history of cancer, cancer therapy, or fertility intervention increases the risk of cancer in the progeny. Aside from hereditary syndromes, available studies have revealed no increased risk of genetic abnormalities, birth defects, or cancers in the children of cancer survivors. Two large registry studies each consisting of over 4000 offspring of cancer survivors showed no statistically increased risk of genetic abnormalities, birth defects, or cancers.[33,34]

Although pregnancy after cancer is achievable and successful, there are documented complications associated with cancer and cancer treatment that a woman

should discuss with her obstetrician when considering pregnancy. On account of the increased risk for complications in this patient population, it would be prudent to seek specialized prenatal care. Moreover, as larger numbers of patients move into their survivorship years and consider having children, data must be collected on which patients are at increased risk of recurrence due to pregnancy.

Cancer During Pregnancy: Concomitant Concern for Woman, Fetus, and Future Fertility

Cancer is the second most common cause of death in women during their reproductive years and a cancer diagnosis is made in approximately 1 of every 1000 pregnancies.[35] The most common cancers diagnosed in pregnant women mirror those in nonpregnant reproductive-age women and include breast cancer, cervical cancer, Hodgkin lymphoma, and melanoma. In addition, the incidence of cancer during pregnancy is expected to increase because of the increasing trend to postpone childbearing. Large prospective studies of women diagnosed with cancer during pregnancy are difficult to execute and few obstetricians, oncologists, and surgeons have extensive experience caring for this patient population. Physicians and patients must navigate a difficult balance between treating the woman for cancer and preserving the well-being of her fetus and future gestations. Thus, it remains critically important for physicians and patients to be knowledgeable about the effects of cancer treatment on pregnancy and the risk to future fertility. Here, we will focus our discussion on breast cancer diagnosed during pregnancy and review what is known about the prognosis, treatment, and the short-term and long-term sequelae for the woman and fetus.

Although antenatal cancer treatment decisions are difficult, it is important to keep in mind that pregnancy does not alter the goal for cancer treatment: local disease control and prevention of metastasis. In general, abdominal and pelvic radiation is contraindicated during pregnancy and therefore systemic therapy will be the focus of this discussion. Most chemotherapeutic agents are rated Food and Drug Administration pregnancy category D (positive evidence for fetal risk), although the timing of therapy often determines the effects on fetal outcome. Specifically, the risk for spontaneous abortion, fetal malformations, and fetal death are greatest when chemotherapeutics are administered during the first trimester, due to the critical period of organogenesis. A review of 163 pregnant women treated for cancer during pregnancy in the first trimester reported a 17% and 25% risk for malformation for single-agent and combination chemotherapy, respectively.[36] During the second and third trimesters, however, most evidence suggests a safer profile. Results from an international registry including 218 women reported that the risk for congenital anomalies, preterm delivery, and growth restriction were not increased in neonates born to mothers treated with chemotherapeutics during the second or third trimester when compared with the general population.[37] The relative safety of chemotherapeutic use in later pregnancy has been attributed to the expression of drug transporters such as multidrug resistance p-glycoprotein and breast cancer resistance protein 1 in fetal tissues.[38] The timing of chemotherapy administration also bears importance near the end of gestation. Systemic therapy should be ceased 3 to 4 weeks before delivery to avoid potential adverse effects on the neonate (myelosuppression and associated complications). Moreover, the timing of chemotherapy has important implications for maternal survival

and fetal development. Fortunately, most evidence suggests a relatively safer profile of systemic agents when administered during the second and third trimesters.

Occurring in approximately 1 in 3000 pregnancies, breast cancer is one of the most studied gestational-associated malignancies and the incidence has more than doubled since the 1960s.[39] Based on retrospective case-control studies, there seems to be no difference in prognosis in women diagnosed with breast cancer during pregnancy compared with nonpregnant age-matched and stage-matched controls.[40] However, owing to the physiological changes in the breast associated with pregnancy, diagnosis is often delayed[41] leading to larger tumor sizes at diagnosis. Furthermore, limited data suggests that termination of pregnancy does not improve the outcome for women diagnosed with breast cancer during pregnancy.[42,43] The University of Texas MD Anderson Cancer Center currently has the largest prospective study (n = 57) of women treated for breast cancer during pregnancy. The protocol uses the FAC regimen (fluorouracil, doxorubicin, and cyclophosphamide) in the adjuvant or neoadjuvant setting. The most recent results from this cohort suggest that breast cancer can be treated with FAC chemotherapy during the second and third trimesters without harm to the children exposed in utero.[44] However, at the time of the published survey, the oldest children were 13 years of age. Thus, the long-term effect of chemotherapy exposure in utero on the fetus' future fertility remains unknown and requires further clinical and basic science investigation.

The treating obstetrician should carefully and continuously monitor the pregnancy (ideally by a Maternal-fetal medicine specialist) in conjunction with the patient's oncologist. Integral to the multidisciplinary approach, patient work-up must include confirmation of gestational age and expected date of delivery. In addition, respiratory maturity may need to be assessed by amniocentesis if preterm delivery is considered. Cancer during pregnancy is associated with significant challenges because of the conflict between optimal maternal treatment and fetal well-being. Although it is an uncommon diagnosis, cancer during pregnancy presents a critical scenario that must be carefully treated by a multidisciplinary team of obstetrician gynecologists, medical oncologists, radiation oncologists, surgeons, pediatricians, genetic counselors, and patient navigators. Moreover, the increasing incidence of cancer during pregnancy presents an emerging and expanding need for the field of Oncofertility.

Conclusion: Role of the Obstetrician and Gynecologist in Partnership With Oncology and Fertility Specialists

A diagnosis of cancer is devastating. For young people before or in their reproductive years, life-saving cancer treatments such as chemotherapy and radiation may threaten their ability to ever conceive or carry biological children. Awareness of this issue has greatly increased over the past decade; thanks to advancements in our ability to address issues on fertility preservation and pregnancy, thus vastly improving the quality of life possible for these patients. In addition, organizations structured around the concept of oncofertility are bringing together a diverse array of specialists to not only provide the most streamlined care for these patients, but also to distribute information on fertility preservation options to patients and providers.

Beyond the pediatric years, many adolescent girls and young women are lost to follow-up in the medical realm and do not become fully reintegrated until a pregnancy brings them in for prenatal care.

Thus, obstetricians and gynecologists, as the primary physicians to many women during their reproductive years, are in a unique position to be at the forefront of the oncofertility initiative by ensuring the proper counseling, referrals, and continuity of care for their patients before, during, and after cancer treatment. Understanding the risks of ovarian failure and reproductive dysfunction caused by cancer treatment and being aware of the fertility preservation options currently available will be crucial knowledge to have in formulating the most appropriate discussion with the patient during this extraordinarily stressful time. By building a long-term physician-patient relationship, obstetricians and gynecologists are the best advocates for their patients in helping them to make the most informed decisions regarding their future fertility and reproductive capacity.

If a new cancer diagnosis presents as a difficult conversation between the physician and patient, then this diagnosis during pregnancy can only be that much more challenging to address. If the woman desires to maintain the pregnancy, all medical decisions made related to the mother's health and future fertility are deeply intertwined with consequences to the fetus. Research on this topic is in its infancy and only time will allow us to tease apart the benefits and harms of each medical decision and its impact on the cancer, the pregnancy, and future fertility in both mother and baby. In these challenging situations, obstetricians play a particularly integral role as patient advocates in seeking the necessary interdisciplinary care, for they may be the first individuals to diagnose the cancer.

As understanding of ovarian biology and fertility threats continues to grow, the ability to preserve reproductive function while eradicating the cancer will undoubtedly improve. The development of oncofertility has spearheaded much progress on this front, and will continue to provide an ideal environment for clinicians, scientists, and other professionals to identify and solve some of the most difficult issues facing fertility today and tomorrow.

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