The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 747

(Replaces Committee Opinion Number 607, August 2014)

Committee on Adolescent Health Care

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care in collaboration with committee members Erin A. Keyser, MD, and Sloane W. Berger-Chen, MD.

Gynecologic Issues in Children and Adolescent Cancer Patients and Survivors

ABSTRACT: The diagnosis of cancer in females younger than 20 years is rare, with the incidence of 17 cases per 100,000 individuals per year in the United States. Although advancements in cancer therapy have dramatically improved childhood cancer survival, gynecologists should be aware of the increased risk of adverse reproductive health effects from each type of therapy. Cancer and its treatment may have immediate or delayed adverse effects on reproductive health. Gynecologists may be consulted for the following issues: pubertal concerns; menstrual irregularities; heavy menstrual bleeding and anemia; sexuality; contraception; ovarian function, including fertility preservation; breast and cervical cancer screening; hormone therapy; and graft-versus-host disease. Approximately 75% of pediatric cancer survivors experience at least one late effect on their health or quality of life. Vigilance in screening and observation on behalf of the health care provider with respect to menstrual irregularities, weight changes, sexual health, growth abnormalities, and bone density are important. In addition to pretreatment fertility conservation counseling, sexually active young women should be thoroughly educated about the risks of becoming pregnant during cancer treatment and strongly encouraged to use effective contraception; contraceptive choices should be discussed with the oncology team. A multidisciplinary approach to cancer survival care is encouraged. This Committee Opinion has been updated to include current data on sexuality and contraception, sexual dysfunction, risk of graft-versus-host disease after stem cell transplant, and updated references and recommendations for fertility preservation.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions:

- Cancer and its treatment may have immediate or delayed adverse effects on reproductive health.
- Gynecologists may be consulted for the following issues: pubertal concerns; menstrual irregularities; heavy menstrual bleeding and anemia; sexuality; contraception; ovarian function, including fertility preservation; breast and cervical cancer screening; hormone therapy; and graft-versus-host disease.
- In addition to pretreatment fertility conservation counseling, sexually active young women should be thoroughly educated about the risks of becoming pregnant during cancer treatment and strongly encouraged to use effective contraception; contraceptive choices should be discussed with the oncology team.
- The science of fertility preservation is a rapidly evolving field; therefore, a referral to a health care provider with experience in oncofertility is recommended to explore the full range of available options.
- Childhood cancer survivors who maintain fertility should be counseled about the health risks to offspring in addition to potential pregnancy-related complications.

- Approximately 75% of pediatric cancer survivors experience at least one late effect on their health or quality of life.
- A multidisciplinary approach to cancer survival care is encouraged.

The diagnosis of cancer in females younger than 20 years is rare, with the incidence of 17 cases per 100,000 individuals per year in the United States (1). Advancements in radiation therapy, chemotherapy, surgery, and multimodal treatment have dramatically improved childhood cancer survival, with the 5-year survival rate reaching almost 80% (2). Although advancements in cancer therapy have dramatically improved childhood cancer survival, gynecologists should be aware of the increased risk of adverse reproductive health effects from each type of therapy. Cancer and its treatment may have immediate or delayed adverse effects on reproductive health. Gynecologists may be consulted for the following issues: pubertal concerns; menstrual irregularities; heavy menstrual bleeding and anemia; sexuality; contraception; ovarian function, including fertility preservation; breast and cervical cancer screening; hormone therapy; and graft-versus-host disease. The purpose of this document is to update gynecologists about the adverse effects of specific cancer treatments and the management of gynecologic issues in young cancer patients and survivors.

Cancer Therapy and Toxicity

Radiation

Radiation therapy is used to treat many kinds of cancer. The adverse effects of radiation therapy vary by site and dose.

Pelvic Irradiation

Pelvic irradiation results in ovarian follicle loss, impaired follicular maturation, and cortical and capsular damage (3). Ovarian insufficiency caused by radiation therapy can lead to infertility and decreased libido in adolescents and young women. Removal of the ovaries from the radiation field by surgical transposition may provide benefit for ovarian tissue preservation (4, 5). Determinants of ovarian dysfunction after radiation treatment include dosage, age, and pubertal development at the time of exposure; the extent of the radiation treatment field; and the concomitant use of chemotherapeutic agents. Ovarian tissue demonstrates a dual sensitivity to radiation therapy and chemotherapy, with reduced future fertility from gonadal failure noted in women who receive more than 5 Gy in a single treatment (Table 1). The Childhood Cancer Survivor Study reported decreased pregnancy rates for those women who had received ovarian or uterine radiation dose greater than 5 Gy (6). Radiation oncologists, therefore, have minimized the toxicity of pelvic irradiation by dividing the dose into multiple smaller doses (termed "fractions"). The dose of fractionated radiation therapy at which ovarian insufficiency occurs immediately after treatment in 97.5% of females is 20.3 Gy (divided into 1.5–2.0 Gy fractions) at birth and decreases to 16.5 Gy at age 20 years of age (7).

Radiation of the uterus results in decreased uterine volume, presumably because of direct effect and atrophy from loss of hormonal function. Hormone therapy has been shown to improve uterine functioning in patients who received less than 25 Gy after puberty (8). The age a patient receives radiation treatment is an important factor, with prepubertal girls experiencing poorer uterine reproductive capacity compared with older patients. Childhood radiation less than 4 Gy appears to have less effect on uterine functioning; however, pregnancy is unlikely after direct uterine radiation (8). Other pelvic organs have a higher tolerance to radiation therapy, with the vaginal epithelium and cervix tolerating doses of 90–100 Gy before fibrosis, dyspareunia, vaginal stenosis, or fistula develop (9).

Cranial Irradiation

Endocrine dysfunction is common in survivors of childhood brain tumors because of the tumor or the treatment (10). Disruption of the hypothalamic–pituitary–ovarian axis is a well-established potential complication found in survivors of central nervous system tumors that can lead to menstrual irregularities, amenorrhea, and infertility. Cranial irradiation also may induce precocious puberty by causing cortical disinhibition of the hypothalamus (11). Survivors of childhood brain tumors who receive radiation therapy directed at the hypothalamus also may

Table 1. Cytotoxic Effect of Ovarian Irradiation

Minimum Ovarian Radiation Dose—Total Dosage (Gy)	Effect
0.6	None
1.5	None in females younger than 40 years
2.5–5.0	Permanent ovarian insufficiency in 60% of females aged 15–40 years; may cause transient amenorrhea

Modified from Friedman DL. The ovary. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, editors. Survivors of childhood and adolescent cancer: a multidisciplinary approach. 3rd ed. New York (NY): Springer International Publishing; 2005. p. 253–65.

experience growth hormone deficiency, hypothyroidism, and adrenocorticotropic hormone deficiency (10, 12).

Chemotherapy

Effects depend on the type of chemotherapeutic agent and cumulative dose. Alkylating agents at chemotherapeutic doses are associated with significant risk of gonadal dysfunction (Box 1). The risk of gonad toxicity is directly proportional to the age and pubertal status of the patient at the time of exposure; that is, the older the patient is at the time of treatment, the higher her risk of early ovarian insufficiency. Ovarian insufficiency can be transient or permanent. Depending on pubertal maturation level, peripubertal exposure can result in delayed or arrested puberty. Postpubertal exposure may lead to oligomenorrhea, amenorrhea, or compromised fertility (6).

Stem Cell Transplant

Graft-versus-host disease is a manifestation of hematopoietic allogenic stem cell transplantation with a high prevalence of 11–48% (13). Vaginal symptoms include pain, itching, burning, dyspareunia, labial fusion, vaginal synechiae, and stenosis. Early identification is the key to preventing long-term sequelae such as vaginal stenosis and hematocolpos; however, there is frequently a delay to diagnosis. A careful examination by a gynecologist is encouraged. A biopsy is generally not necessary for diagnosis (14, 15). Treatment options include high-potency topical steroids and topical estrogen. Significant improvement should be noted 4–8 weeks after treatment is begun (16). With prompt diagnosis and treatment, a patient can return to normal sexual function and can experience limited sequelae. The more advanced the vulvovaginal changes, the more likely the patient may need dilator therapy or surgery for management of severe stenosis and hematocolpos (15, 16).

Human papillomavirus (HPV) related lesions, such as condyloma and cervical dysplasia are frequent in stem cell transplant recipients (13). Therefore, vigilance and routine gynecologic examinations, including the cervix, are recommended. Because these patients are immunosuppressed, the gynecologist should ask about HPV vaccination status and encourage vaccination, if appropriate. The Centers for Disease Control and Prevention (CDC) recommends revaccination of HPV vaccine for females between the ages of 9 and 26 years after hematopoietic stem cell transplant (17). The presence of immunosuppression, like that experienced in patients with human immunodeficiency virus (HIV) infection or organ transplantation, is not a contraindication to HPV vaccination. However, the immune response may be less robust in the immunocompromised patient (18). The three-dose regimen is recommended for immunosuppressed men and women (19).

Box 1. Chemotherapeutic Agents That Increase the Risk of Ovarian Dysfunction

Alkylating agents

- Busulfan
- Carmustine
- Chlorambucil
- Cyclophosphamide
- Ifosfamide
- Lomustine
- Mechlorethamine
- Melphalan
- Procarbazine
- Thiotepa

Nonclassical alkylators

- Dacarbazine
- Temozolomide

Heavy metals

- Carboplatin
- Cisplatin

Modified from Children's Oncology Group. Health link. Healthy living after treatment for childhood cancer. Female health issues after treatment for childhood cancer. Version 4.0. Monrovia (CA): Children's Oncology Group; 2013.

Surgery

Surgical resection of the vagina, uterus, ovaries, or fallopian tubes to treat malignancy will affect fertility. Debulking for abdominal and pelvic tumors, such as Wilms tumor or rhabdomyosarcoma, also may lead to adhesions and infertility, pelvic pain, sexual dysfunction, and fistula formation. In some cases, fertility-sparing surgery can be performed (Fig. 1).

Specific Gynecologic Concerns

Gynecologists should be prepared to manage gynecologic concerns in young cancer patients and survivors. Management may be needed before, during, and after treatment.

Pubertal Development

The patient's age at the time of treatment and the types of treatment recommended for childhood cancer may alter pubertal development. The effects of cancer treatments on pubertal development range from precocious puberty to delayed or arrested puberty to ovarian insufficiency. Central nervous system tumors located in the hypothalamic–pituitary regions may require surgical resection and radiation therapy, which can lead to precocious puberty in some cases and delayed puberty in others. Precocious puberty occurs most frequently in children who were younger at the age of tumor diagnosis (10). Patients who receive more than 24 Gy of cranial irradiation or who are 4 years of age or younger at the start of radiation therapy are at increased risk of early

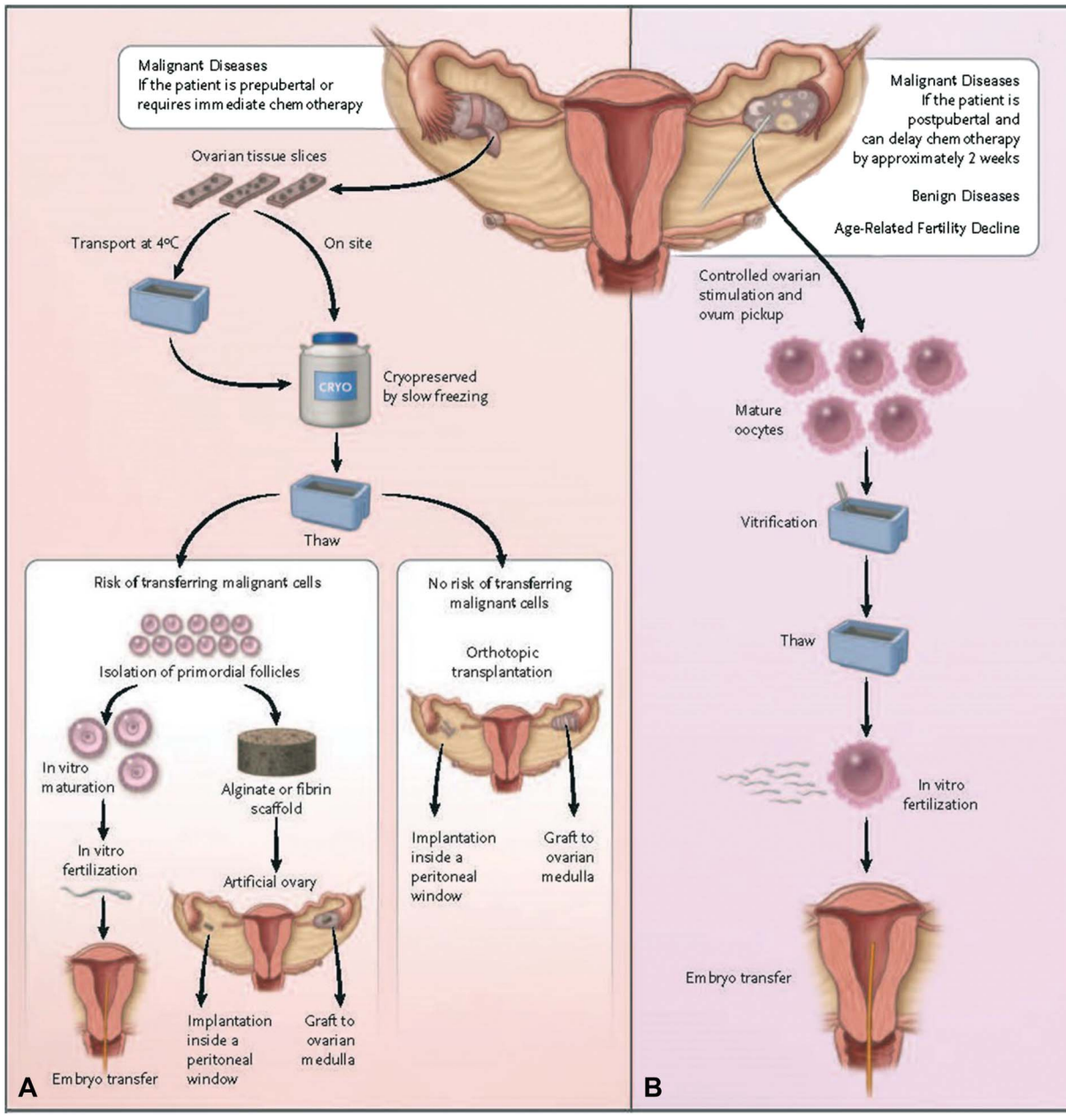

Figure 1. Options for fertility preservation. If the patient is prepubertal or requires immediate chemotherapy (Panel A), ovarian tissue is removed in the form of multiple biopsy specimens (or an entire organ) and cut into cortical strips. The tissue is then cryopreserved by slow freezing on site (or transported to a processing site at a temperature of 4°C). After thawing, if there is no risk of transmitting malignant cells, the ovarian tissue can be grafted to the ovarian medulla (if at least one ovary is still present) or reimplanted inside a specially created peritoneal window. If there is a risk of transmitting malignant cells, ovarian follicles can be isolated and grown in vitro to obtain mature eggs, which can then be fertilized and transferred to the uterine cavity. Isolated follicles may be placed inside a scaffold (alginate or fibrin), creating an artificial ovary that can be grafted to the ovarian medulla or peritoneal window. If the patient is postpubertal and chemotherapy can be delayed for approximately 2 weeks (Panel B), mature oocytes can be removed after ovarian stimulation and vitrified on site. After thawing, they can be inseminated and transferred to the uterine cavity in the form of embryos. This technique can also be used in women with benign diseases or in those with age-related fertility decline. The techniques in Panels A and B can also be combined, with ovarian-tissue cryopreservation followed by controlled ovarian stimulation and vitrification of oocytes. The combined technique theoretically yields a 50 to 60% chance of a live birth. (Reprinted from Donnez J, Dolmans MM. Fertility preservation in women. N Engl J Med 2017;377:1657–65.)

puberty, although early pubertal effects have been reported at doses as low as 18–24 Gy (20).

Adolescent females who are exposed to gonadal toxic therapy may experience a delay in or arrest of pubertal development. Collaboration with a pediatric endocrinologist is recommended for patients in whom growth has been delayed and growth hormone is indicated. Hormonal treatment for induction of puberty and progression of sexual maturation is appropriate for adolescents with arrested pubertal development and should be addressed in collaboration with a pediatric endocrinologist. Rapid, nonphysiologic hormone replacement, such as initiation of a combined oral contraceptive, can lead to consequences such as abnormal breast development and premature closure of the epiphyses. Hormonal replacement is indicated to improve long-term quality of life for adolescents with ovarian insufficiency who have completed the pubertal process.

Heavy Menstrual Bleeding and Anemia

Cancer and its treatments place young women at risk of heavy menstrual bleeding and anemia. Even normal menstrual blood loss may be associated with adverse outcomes in women who are already anemic. There are several options for menstrual management, which are discussed in Committee Opinion No. 606, *Options for Prevention and Management of Heavy Menstrual Bleeding in Adolescent Patients Undergoing Cancer Treatment* (21). Each treatment carries potential risks and benefits. Ideally, therapy for menstrual suppression should be initiated before the onset of cancer treatment after thorough consultation with the young woman, her oncology team, and her gynecologist.

Sexuality and Contraception

Unintended pregnancy is common in the adolescent age group, but pregnancy rates among adolescents and young adults (15–39 years) who are undergoing active cancer treatment are unknown (22). Many adolescents are advised to avoid pregnancy or intercourse during treatment (23). Avoidance of sexual intercourse or abstinence during some stages of treatment, such as when a patient has neutropenia or active mucositis, is recommended and should be discussed with the patient and her oncology team. Chemotherapeutic agents can be excreted in body fluids, including oral and vaginal secretions, for up to 72 hours after treatment. Although there are no data on the effects of chemotherapy agents on sexual partners, the use of barrier methods during oral sex or intercourse or avoidance of sexual activity is recommended to avoid potential partner exposure (24).

Irregular menses during cancer treatment and the focus on fertility preservation before treatment may lead patients and health care providers to incorrectly assume that patients have no chance of pregnancy (23, 25). Obstetrician–gynecologists should counsel patients that irregular bleeding during treatment is a common adverse effect of therapy and is not an indicator of infertility. Female patients tend to overestimate their risk of infertility from treatment, which results in lower use of contraceptives (22). Studies suggest that contraception use in adolescents and young adults undergoing cancer treatment is low (14–21%) (25). Pregnancy during cancer treatment may result in a decision to delay treatment or terminate a pregnancy (26). Furthermore, first-trimester exposure to chemotherapy and radiation is associated with an increased risk of congenital malformations (27). One study reported that survivors of childhood cancer are twice as likely to undergo a therapeutic abortion compared with age-matched controls (28). Women who survive cancer are at three times the increased risk of unintended pregnancy compared with the general population (23). Pretreatment counseling has not been shown to decrease the risk of unintended pregnancy (23). In addition to pretreatment fertility conservation counseling, sexually active young women should be thoroughly educated about the risks of becoming pregnant during cancer treatment and strongly encouraged to use effective contraception; contraceptive choices should be discussed with the oncology team.

The National Comprehensive Cancer Network recommends discussing contraception before the initiation of treatment (29) but has no clear guidelines for oncologists; therefore, obstetrician–gynecologists play a crucial role in addressing contraceptive needs for these patients. The CDC's *U.S. Medical Eligibility Criteria for Contraceptive Use* and Practice Bulletin No. 126, *Management of Gynecologic Issues in Women With Breast Cancer,* offer guidance on the safety of various contraceptive methods based on cancer type (30, 31). These considerations are often multifactorial, and the choice depends on venous thromboembolism risk (eg, presence of a central line), hormonal status of the patient with cancer, or concerns for the development of thrombocytopenia or anemia secondary to treatment, among other issues. Medical eligibility for contraceptive use (https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html) should be carefully examined because each young woman may have special considerations during and after cancer treatment (30). An oncofertility consultation should include discussion of contraception as well as menstrual management. Risks and benefits of contraceptives should be considered along with possible therapeutic effects, such as induced amenorrhea. If a patient is treated with leuprolide acetate for menstrual suppression, this should not be considered a contraceptive method.

Ovarian Insufficiency

Some cancer survivors may experience *ovarian insufficiency*, defined as a loss of ovarian function within 5 years of a diagnosis of cancer. In a study of 3,390 childhood cancer survivors, 6.3% experienced ovarian insufficiency

(32). Risk factors for ovarian insufficiency include older age at diagnosis, Hodgkin lymphoma, increasing ovarian radiation doses, and increasing exposure to alkylating agents. In another study of 2,819 childhood cancer survivors, the risk of nonsurgical ovarian insufficiency before age 40 years was 8% compared with 0.8% in sibling controls (33). The main contributors to ovarian failure risk are age and cumulative dose of chemotherapeutic agents (34). Ovarian insufficiency puts women at risk of psychosexual dysfunction, infertility, and osteoporosis. More data on the utility of monitoring antimüllerian hormones to predict posttreatment fertility and to guide fertility counseling are needed. Serum antimüllerian hormone levels may assist with assessing ovarian reserve at baseline and facilitate patient and family counseling. Most adolescents with ovarian insufficiency are candidates for long-term hormonal treatment at replacement doses to reduce symptoms of estrogen deficiency and long-term risks of fractures and ischemic heart disease (35). See Committee Opinion No. 605, *Primary Ovarian Insufficiency in Adolescents and Young Women,* for more information on diagnosis and evaluation (36).

Breast and Cervical Cancer Screening

A recent systematic review showed a substantially increased risk of breast cancer in women previously treated with chest irradiation, most of whom were treated for Hodgkin lymphoma, with a cumulative incidence of 13–20% by age 40–45 years (37). Routine health screening guidelines for cancer survivors are published and updated by the National Comprehensive Cancer Network (29).

Cervical cytology screening guidelines are the same as for the general population unless the cancer survivor remains immunosuppressed. There are no studies or major society recommendations to guide cervical cytology management in adolescents and young women who are immunocompromised because of cancer treatment. However, the CDC recommends that cervical cytology screening for sexually active women who are immunocompromised due to HIV infection should be initiated within the first year after diagnosis, even if they are younger than 21 years (38). There is not enough evidence to determine whether adolescent females and young women who are immunocompromised due to other causes should undergo cervical cytology screening at the onset of sexual activity or wait until age 21 years. Human papillomavirus vaccination should be encouraged. The three-dose regimen is recommended for immunosuppressed men and women (19).

Sexual Dysfunction

Female cancer survivors, at any age, are at risk of sexual dysfunction after treatment. Relationships, body image, and sexuality are concerns that are defining characteristics of many adolescents in normal health, and they may be of even greater importance after a cancer diagnosis and during treatment (39). Sexual function is important for quality of life and maintaining intimate partner relationships (40, 41). Cancer treatments and their sequalae can result in endocrine dysfunction and physical changes that may affect a woman's body image, all of which can contribute to loss of sexual identity, function, and desire. Several cancer treatments can lead to vulvovaginal atrophy for which vaginal moisturizers and lubricants are safe and effective. Posttreatment options are dependent on cancer type and may include hormone replacement, topical vaginal estrogen, dehydroepiandrosterone creams, topical testosterone, and ospemifene (42–45). For more information on use of vaginal estrogen in breast cancer survivors, see Committee Opinion No. 659, *The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer* (46). Other treatments, such as laser therapy, have been used; however, data are lacking on their long-term effectiveness, especially in the adolescent population.

In patients who are not currently sexually active, but plan to be, consideration of dilator therapy is reasonable, especially if significant atrophy or scarring is present. Survivors should be evaluated for bladder damage from medication or radiation, which may lead to recurrent cystitis and functional voiding difficulties (47). Obstetrician–gynecologists should be prepared to address and manage sexual dysfunction after cancer treatment, including in adolescent patients.

Future Fertility and Fertility Preservation

In the largest study of childhood cancer survivors, the relative risk of pregnancy among adult cancer survivors who were not surgically sterilized was 0.81 (95% CI, 0.73–0.90) compared with their sibling cohort (6). Reduced fertility was associated with hypothalamic or pituitary irradiation at dose greater than or equal to 30 Gy, ovarian–uterine irradiation at dose greater than 5 Gy, or increased use of alkylating agents (6). See Box 1 for a list of alkylating agents.

When compared with gonadotropin levels, antimüllerian hormone level may be a useful screening tool for assessing ovarian reserve in survivors of childhood cancer, although more long-term data on its use are needed (48). A study of 53 females demonstrated the effectiveness of antimüllerian hormone level as a screening tool for assessing ovarian reserve in female childhood cancer survivors, although the authors noted the limitations of their cross-sectional study design (49). Other data indicate that although antimüllerian hormone may serve as an indicator of ovarian reserve, it may not be an accurate predictor of fertility potential (50). In girls, adolescent females, and women who might be at risk of infertility with cancer treatment, options for fertility preservation should be discussed before treatment. For patients who will be treated with

pelvic irradiation, oophoropexy to move the gonads away from the radiation field may have a protective effect (51).

Cryopreservation of oocytes or embryos also may be offered before cancer treatments if there is adequate time and a safe method for ovarian stimulation (52) (see Fig. 1 for fertility preservation options). Ovarian tissue extraction and cryopreservation have been shown to have some success with posttreatment autotransplantation after chemotherapy. Live births have been reported in patients who had spontaneous pregnancy, as well as in those treated with assisted reproductive technology (53). Cryopreservation of ovarian tissue with autologous transplantation or maturation of primordial follicles has been successful (54). However, cancer recurrence in the autologous transplant is a concern. The science of fertility preservation is a rapidly evolving field; therefore, a referral to a health care provider with experience in oncofertility is recommended to explore the full range of available options. Additionally, there are ethical issues that involve minors and their ability to give voluntary informed consent, assent, or refusal for procedures or experimental treatments related to fertility preservation.

For young women who have completed sexual development, gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate, have been used to induce ovarian quiescence to preserve ovarian function and fertility after cytotoxic treatment. Leuprolide acetate is not recommended for prepubertal girls. There still is no conclusive evidence that demonstrates efficacy of GnRH agonists, and studies are primarily observational regarding their effectiveness in fertility preservation. The American Society for Reproductive Medicine and the National Comprehensive Cancer network recommend GnRH agonists for prevention of heavy menstrual bleeding (55). Several meta-analyses have shown statistically significant improved outcomes in return to menses, increased time until ovarian insufficiency, and pregnancy outcomes (56–64). The use of GnRH agonists should be considered and discussed with premenopausal patients who will be treated with chemotherapeutic agents. Because GnRH agonists have mixed results in fertility preservation with trends toward more favorable outcomes, GnRH agonist therapy may be recommended as an adjuvant to chemotherapy. A meta-analysis of females 14–45 years of age demonstrated that cotreatment with GnRH agonists during chemotherapy was associated with increased odds of maintaining ovarian function and achieving pregnancy after treatment (34). Gynecologists may consider the use of add-back therapy in patients experiencing vasomotor symptoms during GnRH agonist use. Potential therapies that have shown efficacy in adolescents with endometriosis on a GnRH agonist include norethindrone 5 mg daily or conjugated equine estrogen 0.625 with norethindrone 2.5 mg or 5 mg (65, 66). However, recommendations for bone density effects have not been established in the adolescent population. Combining modalities to preserve ovarian function may increase the likelihood of maintaining future fertility (56, 67–70).

Pregnancy Outcomes

A history of cancer and cancer treatment may affect the outcome of future pregnancies. Childhood cancer survivors who maintain fertility should be counseled about the health risks to offspring in addition to potential pregnancy-related complications. Investigators from the Childhood Cancer Survivors Study found that compared with sibling-matched controls, childhood cancer survivors were less likely to become pregnant (71). Offspring born to survivors with germline cancer–predisposing mutations had a greater risk of cancer (72). Several studies have demonstrated that chemotherapy does not adversely affect fetal growth and development or uterine function; however, cardiac decompensation may occur in pregnant women previously treated with anthracycline antibiotics, such as doxorubicin or daunorubicin (71). In long-term follow-up studies of the pregnancies of childhood cancer survivors who received radiation therapy, the risk of congenital malformations, genetic disorders, and cancer was the same as for their sibling controls; however, the risk of premature birth and low birth weight was increased compared with sibling controls when specifically exposed to pelvic irradiation (6). Other adverse pregnancy outcomes, such as fetal malposition, abnormal placentation, maternal pregnancy-induced hypertensive disorders, postpartum hemorrhage, and uterine rupture, also have been reported (73–75). Survivors of leukemia and lymphoma may be at higher risk of preterm birth and low-birth-weight infants (76). Data do not support a higher risk of spontaneous abortion, maternal diabetes, or anemia during pregnancy. Those patients diagnosed with breast cancer should delay pregnancy until 24 months posttreatment because of an increased likelihood of recurrence during this period. For patients using endocrine management for breast cancer, current studies are evaluating the effect of interruption in therapy to allow for pregnancy (47, 77).

Follow-up

Approximately 75% of pediatric cancer survivors experience at least one late effect on their health or quality of life. Endocrine dysfunction is a common late effect of chemotherapy or the disease itself (47). This can result in thyroid disease, precocious puberty, rapid tempo of puberty, hypogonadism, ovarian insufficiency, infertility, metabolic syndrome, and impaired bone health. Pretreatment and posttreatment antimüllerian hormone level continues to be investigated as a marker to monitor ovarian reserve after cancer treatments.

Vigilance in screening and observation on behalf of the health care provider with respect to menstrual irregularities, weight changes, sexual health, growth abnormalities, and bone density are important. A multidisciplinary approach to cancer survival care is encouraged (57, 78).

References

1. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, et al, editors. Childhood cancer by site: incidence, survival and mortality. In: SEER cancer statistics review, 1975-2014. Bethesda (MD): National Cancer Institute; 2017.
2. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 2009;27: 2308–18.
3. Friedman DL. The ovary. In: Schwartz CL, Hobbie WL, Constine LS, Ruccione KS, editors. Survivors of childhood and adolescent cancer: a multidisciplinary approach. 3rd ed. New York (NY): Springer International Publishing; 2005. p. 253–65.
4. Moawad NS, Santamaria E, Rhoton-Vlasak A, Lightsey JL. Laparoscopic ovarian transposition before pelvic cancer treatment: ovarian function and fertility preservation. J Minim Invasive Gynecol 2017;24:28–35.
5. Chan JL, Wang ET. Oncofertility for women with gynecologic malignancies. Gynecol Oncol 2017;144:631–6.
6. Green DM, Kawashima T, Stovall M, Leisenring W, Sklar CA, Mertens AC, et al. Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 2009;27:2677–85.
7. Wallace WH, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. Int J Radiat Oncol Biol Phys 2005; 62:738–44.
8. Teh WT, Stern C, Chander S, Hickey M. The impact of uterine radiation on subsequent fertility and pregnancy outcomes. Biomed Res Int 2014;2014:482968.
9. Kirchheiner K, Nout RA, Lindegaard JC, Haie-Meder C, Mahantshetty U, Segedin B, et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio (chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE. EMBRACE Collaborative Group. Radiother Oncol 2016; 118:160–6.
10. Shalitin S, Gal M, Goshen Y, Cohen I, Yaniv I, Phillip M. Endocrine outcome in long-term survivors of childhood brain tumors. Horm Res Paediatr 2011;76:113–22.
11. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys 2009;73: 1304–12.
12. Rohrer TR, Beck JD, Grabenbauer GG, Fahlbusch R, Buchfelder M, Dorr HG. Late endocrine sequelae after radiotherapy of pediatric brain tumors are independent of tumor location. J Endocrinol Invest 2009;32: 294–7.
13. Hirsch P, Leclerc M, Rybojad M, Petropoulou AD, Robin M, Ribaud P, et al. Female genital chronic graft-versus-host disease: importance of early diagnosis to avoid severe complications. Transplantation 2012;93:1265–9.
14. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11:945–56.
15. Smith Knutsson E, Bjork Y, Broman AK, Helstrom L, Levin Jakobsen AM, Nilsson O, et al. Genital chronic graft-versus-host disease in females: a cross-sectional study. Biol Blood Marrow Transplant 2014;20:806–11.
16. Stratton P, Turner ML, Childs R, Barrett J, Bishop M, Wayne AS, et al. Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. Obstet Gynecol 2007;110:1041–9.
17. Centers for Disease Control and Prevention. Altered immunocompetence. General best practice guidelines for immunization: best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Atlanta (GA): CDC; 2017.
18. Levin MJ, Moscicki AB, Song LY, Fenton T, Meyer WA III, Read JS, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. IMPAACT P1047 Protocol Team. J Acquir Immune Defic Syndr 2010; 55:197–204.
19. Human papillomavirus vaccination. Committee Opinion No. 704. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e173–8.
20. Armstrong GT, Whitton JA, Gajjar A, Kun LE, Chow EJ, Stovall M, et al. Abnormal timing of menarche in survivors of central nervous system tumors: a report from the Childhood Cancer Survivor Study. Cancer 2009;115:2562–70.
21. Options for prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment. Committee Opinion No. 606. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014; 124:397–402.
22. Murphy D, Klosky JL, Termuhlen A, Sawczyn KK, Quinn GP. The need for reproductive and sexual health discussions with adolescent and young adult cancer patients. Contraception 2013;88:215–20.
23. Quinn MM, Letourneau JM, Rosen MP. Contraception after cancer treatment: describing methods, counseling, and unintended pregnancy risk. Contraception 2014;89: 466–71.
24. Kelvin JF, Steed R, Jarrett J. Discussing safe sexual practices during cancer treatment. Clin J Oncol Nurs 2014;18:449–53.
25. Fridgen O, Sehovic I, Bowman ML, Reed D, Tamargo C, Vadaparampil S, et al. Contraception: the need for expansion of counsel in adolescent and young adult (AYA) cancer care. J Cancer Educ 2017;32:924–32.

26. Gambino A, Gorio A, Carrara L, Agoni L, Franzini R, Lupi GP, et al. Cancer in pregnancy: maternal and fetal implications on decision-making. Eur J Gynaecol Oncol 2011;32:40–5.

27. Pereg D, Koren G, Lishner M. Cancer in pregnancy: gaps, challenges and solutions. Cancer Treat Rev 2008;34:302–12.

28. Green DM, Whitton JA, Stovall M, Mertens AC, Donaldson SS, Ruymann FB, et al. Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002;187:1070–80.

29. National Comprehensive Cancer Network. Adolescent and young adult (AYA) oncology. Version 2.2018. NCCN Clinical Practice Guidelines in Oncology [after login]. Fort Washington (PA): NCCN; 2017.

30. Tepper NK, Krashin JW, Curtis KM, Cox S, Whiteman MK. Update to CDC's U.S. medical eligibility criteria for contraceptive use, 2016: revised recommendations for the use of hormonal contraception among women at high risk for HIV infection. MMWR Morb Mortal Wkly Rep 2017; 66:990–4.

31. Management of gynecologic issues in women with breast cancer. Practice Bulletin No. 126. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;119: 666–82.

32. Chemaitilly W, Mertens AC, Mitby P, Whitton J, Stovall M, Yasui Y, et al. Acute ovarian failure in the childhood cancer survivor study. J Clin Endocrinol Metab 2006;91:1723–8.

33. Sklar CA, Mertens AC, Mitby P, Whitton J, Stovall M, Kasper C, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. J Natl Cancer Inst 2006;98:890–6.

34. Clowse ME, Behera MA, Anders CK, Copland S, Coffman CJ, Leppert PC, et al. Ovarian preservation by GnRH agonists during chemotherapy: a meta-analysis. J Womens Health (Larchmt) 2009;18:311–9.

35. Rafique S, Sterling EW, Nelson LM. A new approach to primary ovarian insufficiency. Obstet Gynecol Clin North Am 2012;39:567–86.

36. Primary ovarian insufficiency in adolescents and young women. Committee Opinion No. 605. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014; 124:193–7.

37. Henderson TO, Amsterdam A, Bhatia S, Hudson MM, Meadows AT, Neglia JP, et al. Surveillance for breast cancer in women treated with chest radiation for a childhood, adolescent or young adult cancer: a report from the children's oncology group. Ann Intern Med 2010;152:444–55; W144–54.

38. Cervical cancer screening and prevention. Practice Bulletin No. 168. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;128:e111–30.

39. Kelly D. Developing age appropriate psychosexual support for adolescent cancer survivors: a discussion paper. J Sex Med 2013;10(suppl):133–8.

40. Sexual health. Committee Opinion No. 706. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e42–7.

41. Lindau ST, Abramsohn EM, Matthews AC. A manifesto on the preservation of sexual function in women and girls with cancer. Am J Obstet Gynecol 2015;213:166–74.

42. Melisko ME, Goldman ME, Hwang J, De Luca A, Fang S, Esserman LJ, et al. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial. JAMA Oncol 2017;3:313–9.

43. Barton DL, Sloan JA, Shuster LT, Gill P, Bearden JD, Johnson DB, et al. Impact of vaginal dehydroepiandosterone (DHEA) on vaginal symptoms in female cancer survivors: trial N10C1 (Alliance) [abstract]. J Clin Oncol 2014;32: 9507.

44. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. Maturitas 2014;78:91–8.

45. Constantine G, Graham S, Koltun WD, Kingsberg SA. Assessment of ospemifene or lubricants on clinical signs of VVA. J Sex Med 2014;11:1033–41.

46. The use of vaginal estrogen in women with a history of estrogendependent breast cancer. Committee Opinion No. 659. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;127:e93–6.

47. Dickerman JD. The late effects of childhood cancer therapy [published erratum appears in Pediatrics 2007;119:1045]. Pediatrics 2007;119:554–68.

48. Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2013;31:2500–10.

49. Lunsford AJ, Whelan K, McCormick K, McLaren JF. Antimullerian hormone as a measure of reproductive function in female childhood cancer survivors. Fertil Steril 2014;101: 227–31.

50. Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, et al. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. JAMA 2017;318:1367–76.

51. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol 2003;188:367–70.

52. Oocyte cryopreservation. Committee Opinion No. 584. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:221–2.

53. Meirow D, Ra'anani H, Shapira M, Brenghausen M, Derech Chaim S, Aviel-Ronen S, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. Fertil Steril 2016;106:467–74.

54. Lawrenz B, Rothmund R, Neunhoeffer E, Huebner S, Henes M. Fertility preservation in prepubertal girls prior to chemotherapy and radiotherapy–review of the literature. J Pediatr Adolesc Gynecol 2012;25:284–8.

55. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. Practice Committee of American Society for Reproductive Medicine. Fertil Steril 2013;100:1214–23.

56. Hickman LC, Valentine LN, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a review of the potential role for gonadotropin-releasing hormone agonists. Am J Obstet Gynecol 2016;215:415–22.

57. Blumenfeld Z, Zur H, Dann EJ. Gonadotropin-releasing hormone agonist cotreatment during chemotherapy may increase pregnancy rate in survivors. Oncologist 2015;20: 1283–9.

58. Elgindy E, Sibai H, Abdelghani A, Mostafa M. Protecting ovaries during chemotherapy through gonad suppression: a systematic review and meta-analysis. Obstet Gynecol 2015;126:187–95.

59. Gerber B, Ortmann O. Prevention of Early Menopause Study (POEMS): is it possible to preserve ovarian function by gonadotropin releasing hormone analogs (GnRHa)? Arch Gynecol Obstet 2014;290:1051–3.

60. Lambertini M, Ceppi M, Poggio F, Peccatori FA, Azim HA Jr, Ugolini D, et al. Ovarian suppression using luteinizing hormone-releasing hormone agonists during chemotherapy to preserve ovarian function and fertility of breast cancer patients: a meta-analysis of randomized studies. Ann Oncol 2015;26:2408–19.

61. Lambertini M, Boni L, Michelotti A, Gamucci T, Scotto T, Gori S, et al. Ovarian suppression with triptorelin during adjuvant breast cancer chemotherapy and long-term ovarian function, pregnancies, and disease-free survival: a randomized clinical trial. GIM Study Group. JAMA 2015;314: 2632–40.

62. Munhoz RR, Pereira AA, Sasse AD, Hoff PM, Traina TA, Hudis CA, et al. Gonadotropin-releasing hormone agonists for ovarian function preservation in premenopausal women undergoing chemotherapy for early-stage breast cancer: a systematic review and meta-analysis. JAMA Oncol 2016;2:65–73.

63. Chen H, Li J, Cui T, Hu L. Adjuvant gonadotropin-releasing hormone analogues for the prevention of chemotherapy induced premature ovarian failure in premenopausal women. Cochrane Database of Systematic Reviews 2011, Issue 11. Art. No.: CD008018. DOI: 10. 1002/14651858.CD008018.pub2.

64. Poorvu PD, Barton SE, Duncan CN, London WB, Laufer MR, Lehmann LE, et al. Use and effectiveness of gonadotropin-releasing hormone agonists for prophylactic menstrual suppression in postmenarchal women who undergo hematopoietic cell transplantation. J Pediatr Adolesc Gynecol 2016;29:265–8.

65. Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. Obstet Gynecol 2002;99:709–19.

66. Kiesel L, Schweppe KW, Sillem M, Siebzehnrubl E. Should add-back therapy for endometriosis be deferred for optimal results? Br J Obstet Gynaecol 1996;103 suppl:15–7.

67. Garrido-Oyarzun MF, Castelo-Branco C. Controversies over the use of GnRH agonists for reduction of chemotherapy-induced gonadotoxicity. Climacteric 2016; 19:522–5.

68. Levine JM, Kelvin JF, Quinn GP, Gracia CR. Infertility in reproductive-age female cancer survivors. Cancer 2015;121: 1532–9.

69. Moore HC, Unger JM, Phillips KA, Boyle F, Hitre E, Porter D, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. POEMS/S0230 Investigators. N Engl J Med 2015;372:923–32.

70. Raffoul L, Captio C, Sarnacki S. Fertility considerations and the pediatric oncology patient. Semin Pediatr Surg 2016;25: 318–22.

71. Hudson MM. Reproductive outcomes for survivors of childhood cancer. Obstet Gynecol 2010;116:1171–83.

72. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, et al. Cancer survivorship–genetic susceptibility and second primary cancers: research strategies and recommendations. J Natl Cancer Inst 2006;98:15–25.

73. Norwitz ER, Stern HM, Grier H, Lee-Parritz A. Placenta percreta and uterine rupture associated with prior whole body radiation therapy. Obstet Gynecol 2001;98:929–31.

74. Green DM, Lange JM, Peabody EM, Grigorieva NN, Peterson SM, Kalapurakal JA, et al. Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. J Clin Oncol 2010;28:2824–30.

75. Lie Fong S, van den Heuvel-Eibrink M, Eijkemans MJ, Schipper I, Hukkelhoven CW, Laven JS. Pregnancy outcome in female childhood cancer survivors. Hum Reprod 2010;25:1206–12.

76. Shliakhtsitsava K, Romero SAD, Dewald SR, Su HI. Pregnancy and child health outcomes in pediatric and young adult leukemia and lymphoma survivors: a systematic review. Leuk Lymphoma 2018;59:381–97.

77. Chueh HW, Yoo JH. Metabolic syndrome induced by anticancer treatment in childhood cancer survivors. Ann Pediatr Endocrinol Metab 2017;22:82–9.

78. Bedoschi G, Navarro PA, Oktay K. Chemotherapy-induced damage to ovary: mechanisms and clinical impact. Future Oncol 2016;12:2333–44.

Published online on July 25, 2018.

American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

Gynecologic issues in children and adolescent cancer patients and survivors. ACOG Committee Opinion No. 747. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e67–77.

This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on www.acog.org or by calling the ACOG Resource Center.

While ACOG makes every effort to present accurate and reliable information, this publication is provided "as is" without any warranty of accuracy, reliability, or otherwise, either express or implied. ACOG does not guarantee, warrant, or endorse the products or services of any firm, organization, or person. Neither ACOG nor its officers, directors, members, employees, or agents will be liable for any loss, damage, or claim with respect to any liabilities, including direct, special, indirect, or consequential damages, incurred in connection with this publication or reliance on the information presented.

All ACOG committee members and authors have submitted a conflict of interest disclosure statement related to this published product. Any potential conflicts have been considered and managed in accordance with ACOG's Conflict of Interest Disclosure Policy. The ACOG policies can be found on acog.org. For products jointly developed with other organizations, conflict of interest disclosures by representatives of the other organizations are addressed by those organizations. The American College of Obstetricians and Gynecologists has neither solicited nor accepted any commercial involvement in the development of the content of this published product.

The content of this publication is the sole responsibility of the authors and does not necessarily reflect the views or policies of the Department of Defense (DoD) or the Departments of the Army, Navy, or Air Force. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.