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Clinical Guidelines

Cancer and contraception

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Abstract

As a result of advances in cancer diagnosis and treatment, young women within the reproductive-aged group are now more likely to survive cancer. Reproductive-aged women with cancer may be interested in deferring pregnancy either temporarily or permanently at cancer diagnosis, during therapy or after treatment. Currently, there are limited guidelines to aide clinicians in managing the contraceptive needs in this special population. After reviewing the evidence regarding the safety and efficacy of available methods of contraception for women who have been diagnosed with cancer, the Society of Family Planning recommends that women of childbearing age who are being treated for cancer avoid combined hormonal contraceptive methods (containing estrogen and progestin) when possible because they may further increase the risk of venous thromboembolism (VTE) (Level A). The copper T380A intrauterine device, a highly effective, reversible, long-acting, hormone-free method, should be considered the first-line contraceptive option for women with a history of breast cancer (Level A), although for women being treated with tamoxifen, the levonorgestrel-containing intrauterine system (IUS) which decreases endometrial proliferation may be preferable (Level B). Women who develop anemia may benefit from use of a progestin-containing contraceptive (Level A). Women who develop osteopenia or osteoporosis following chemotherapy should avoid the progestin-only contraceptive injection (Level B).

More information is needed in many areas. There are insufficient data to evaluate the risk of VTE when progestin-only contraceptives are used by women at high risk of VTE. Information is also needed on whether the levonorgestrel-containing IUS affects the risk of breast cancer recurrence and whether hormonal contraceptives affect the risk of breast cancer among women who have received chest wall, or "mantle field," radiation. Finally, studies of the safety and effectiveness of IUS use by women who are immunosuppressed and studies of whether progestin-only contraceptives affect the risk of fracture among cancer survivors or, more generally, women with osteopenia would be useful.

Keywords: Contraception; Cancer

Background

Each year in the United States, an estimated 740,000 women are diagnosed with cancer [1]. It is now estimated that there are 11.4 million cancer survivors in the United States [2], and the number of cancer survivors is likely to grow. Screening allows earlier detection of cancer, and new treatments improve survival. Indeed, 80% of women diagnosed with cancer before the age of 50 years will survive for at least 5 years [3]. Unfortunately, many women who have survived cancer continue to feel their reproductive health needs are unmet [4,5]. Cancer survivors have been found to have limited awareness of available contraceptives [6], in part because many cancer units, including those that care for adolescents, do not routinely discuss contraception with their sexually active patients [7]. Population-representative data on the prevalence of unintended pregnancy among cancer survivors are not currently available. However, in the United States, cancer survivors aged 15–30 were more likely to terminate a pregnancy than age-matched controls [8]. Similarly, a recent Danish study found that cancer survivors were slightly more likely to terminate a pregnancy than their sisters or population-based controls [9].

Contraception is key to preventing unintended pregnancy. However, all contraception is not the same. The World Health Organization has classified contraception into four tiers based on efficacy. Long-acting contraceptive methods including sterilization, implants and intrauterine devices (IUDs) are ranked as the most effective methods (tier 1). Other short-term contraceptive methods, which include combined estrogen and progestin methods with various delivery systems (tier 2) and barrier (tier 3) and behavioral methods (tier 4), may be suboptimal for cancer patients due to decreased efficacy and compliance or hormones which may be relatively or absolutely contraindicated in cancer patients [10].

While chemotherapy and radiation reduce fertility and may cause ovarian failure [11], many cancer survivors remain fertile [12,13]. Among childhood cancer survivors,

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cancer treatment is thought to reduce fertility by 10%–25%, depending on the type of treatment received [14]. Norwegian data suggest that in the 10 years following a cancer diagnosis, women who are diagnosed with cancer are about half as likely as age-matched women without cancer diagnoses to become pregnant [15]. However, the fertility of young women treated with gonadotropin-releasing hormone agonists during chemotherapy frequently returns spontaneously after treatment [16]. Furthermore, in a study of young survivors of breast cancer, 67% remained fertile [13].

Reproductive-aged, fertile women undergoing cancer treatment are generally advised to avoid pregnancy due to concerns of the teratogenic effects of chemotherapy or radiation. After treatment, many women may choose to prevent pregnancy. And breast cancer survivors are advised to avoid pregnancy for 3 years following cancer treatment [17] due to concerns that pregnancy-related hormonal changes may increase the risk of recurrence. This guideline has therefore been developed for clinicians caring for reproductive-aged women who need contraceptives after they have been diagnosed with or treated for cancer.

It is important to explore the patient's understanding of her prognosis, risk of recurrence and fertility, as some women may believe that they are infertile despite resumption of normal menses following treatment for cancer. Uncertainties regarding future fertility, pregnancy outcomes and cancer recurrence can be challenging for patients and their clinicians. At times, the goals of cancer care may conflict with a patient's reproductive goals. However, with appropriate counseling and preventive measures, this conflict may be minimized. Multidisciplinary care involving, as needed, the patient's primary care provider, oncologist, obstetrician and family planning specialist may be helpful in providing individualized recommendations regarding contraception, fertility and pregnancy.

Clinical questions and recommendations

1. How is fertility assessed in cancer survivors? Does this patient need contraception?

When considering whether a woman who has survived cancer may need contraception, clinicians must be aware that the usual signs of fertility may not be reliable in women who have undergone cancer treatments. Pregnancy has been reported in cancer survivors despite amenorrhea and follicle-stimulating hormone levels suggestive of menopause [16,18]. Thus, the absence of menstruation does not necessarily indicate lack of ovarian function [19]. Since menstrual activity is not a reliable index of ovarian function, various biochemical tests (including follicle-stimulating hormone level, inhibin A or B levels, or anti-Mullerian hormone) and biophysical tests (including vaginal ultrasonography assessment to evaluate antral follicle count and ovarian volume) have been used to estimate ovarian reserve. Currently, anti-Mullerian hormone levels are thought to be the best predictor of a woman's future fertility [20–22]. Identification of which women are fertile after chemotherapy remains an area of active research.

2. How does the primary cancer type affect contraceptive options?

Cancer type influences recommendations regarding contraception. This is especially true for breast cancer or other hormonally mediated cancers. For women with breast cancer, exogenous estrogen and progestins are not recommended due to concerns that they may increase the risk of cancer recurrence. Estrogen and progestin receptor status affect tumor growth and prognosis [23]; thus, estrogen receptor blockade is a key component of breast cancer treatment. Data are lacking on the extent to which use of estrogen-containing contraceptives by a breast cancer survivor may increase the likelihood of breast cancer recurrence. Additionally, data regarding the impact of postmenopausal hormone replacement therapy are conflicting. Two trials evaluating the use of postmenopausal hormone therapy by breast cancer survivors were stopped early due to safety concerns [24,25]. In contrast, eight observational studies showed no increased risk of cancer recurrence among breast cancer survivors who took postmenopausal hormone therapy [26].

The role of progestins in breast cancer in both pre- and postmenopausal women remains understudied [27]. Animal studies have indicated that progestins induce growth and metastasis of breast cancer [28,29]. Thus, use of systemic progestin-containing contraceptives is generally not advised for women who have a prior diagnosis of breast cancer. Conversely, oral medroxyprogesterone acetate has shown to have some benefit as a chemotherapeutic agent [30,31], and in the general population, progestin-only contraceptives have not been associated with an increased risk of breast cancer [32–36].

Given the above-mentioned controversies and concerns regarding use of exogenous hormones by women who have been diagnosed with breast cancer, the copper T380A, the most effective hormone-free reversible contraceptive, should be considered the preferred option for breast cancer survivors [37,38]. Additional studies are needed to evaluate the safety of progestins in hormonally breast cancer, as well as the effect of exogenous hormones on hormonally mediated cancers in premenopausal women.

For women being treated with tamoxifen, which can cause endometrial proliferation and even endometrial cancer, the levonorgestrel-containing intrauterine system (IUS) may be optimal for both contraceptive and endometrial effects, as it decreases both endometrial proliferation and the need for investigation of vaginal bleeding. While several studies [39–43] that examined use of the levonorgestrel IUS by women whose breast cancer was being treated with tamoxifen did not find a higher risk of breast cancer recurrence, one subgroup analysis of women who were using a levonorgestrel IUS at the time of breast cancer diagnosis and who

continued using their IUS (n=38) found that they were significantly more likely to have a recurrence of breast cancer than women who did not have an IUS at the time they were diagnosed [adjusted hazard ratio, 3.4; 95% confidence interval (CI), 1.01–11.35] [42]. More research is therefore needed to determine the long-term safety of the levonorgestrel IUS by women with a history of breast cancer.

3. How does the increased risk of venous thromboembolism (VTE) affect contraceptive selection?

Both cancer [44,45] and estrogen [46,47] are independent risk factors for VTE. Cancer patients with VTE have twice the mortality of those who do not experience VTE [48,49]. Indeed, thromboembolism is one of the leading causes of death in cancer patients [50]. Lung, lymph, gynecologic and genitourinary cancers pose a higher-than-average risk of VTE, and gastric and pancreatic cancers pose a particularly high risk of VTE (i.e., rates are more than three times the population average). In contrast, breast and colorectal cancers are less commonly complicated by VTE [45].

Due to the increased risk of VTE, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend that women with active cancer or who have been treated for cancer in the last 6 months (other than nonmelanoma skin cancer) avoid combined hormonal contraceptive methods (Category 4) [51]. Progestin-only contraceptives increase the risk of VTE much less than estrogen-containing products [52], and the CDC posit that the benefits outweigh the perceived risks (Category 2) [51].The available literature is insufficient to determine if progestin-only contraceptives increase the likelihood of VTE among high-risk women [53]. Of several case–control studies that have examined the association between progestin-only contraceptives and VTE, only one found a significantly increased VTE risk [47,52,54–60]: A recent report from the Netherlands' Multiple Environmental and Genetic Assessment of risk factors for VTE case–control study found that women using depot-medroxyprogesterone acetate (DMPA) had a higher risk of VTE than nonusers of hormonal contraception (odds ratio=3.6, 95% CI 1.8–7.1) [61]. Concern has also been raised by older studies of progestin doses higher than those used for contraception which showed an increased risk of VTE among progestin users than among age-matched controls who were not using progestin [58,59]. In general, the available data do not demonstrate that progestin-only contraceptives increase the risk of VTE [52,62].

4. How do common complications of cancer treatment impact contraceptive selection?

Anemia

For women affected by anemia, use of hormonal contraceptives for their noncontraceptive benefits may be warranted. Rates of anemia are particularly high for women with lung cancer (77% of whom develop anemia) and gynecologic cancer (81% of whom develop anemia) [63]. As women with cancer-induced anemia have decreased functional capacity and quality of life and shorter survival, efforts to minimize menstrual blood loss with the use of a progestin-containing contraceptive [64], particularly the levonorgestrel IUS [65], may be warranted. The copper T380A may increase menstrual blood loss in some women [66], and the implant can cause an unpredictable bleeding profile throughout the course of its use [67]. While the clinical implications of these changes in bleeding patterns are unknown, use of other methods of contraception may be advisable in women with severe anemia, particularly if other methods may improve hematologic status.

Osteoporosis

Osteoporosis is a common complication of chemotherapy [68,69]. For patients with preexisting bone loss, the use of DMPA should be considered with caution; however, the effects of DMPA on bone mineral density have been found to be reversible [70]. One database study conducted in the general population in the United Kingdom demonstrated that DMPA use was associated with a slight increase in the risk of fracture; this association was not seen in a systematic review of randomized controlled trials of contraception and fracture [71–73]. However at present, there are limited data regarding use of DMPA by women with multiple risk factors for osteoporotic fracture [74]. Contraceptive implants have been shown to affect radial [75,76] and ulnar bone mineral density [77]; however, whether this finding is associated with an increased risk of fractures is unknown. The levonorgestrel IUS does not adversely affect bone mineral density [78]. In contrast, estrogen-containing contraceptives may be advantageous for women who are osteopenic, but study results are mixed [79,80].

Immunosuppression

There are limited data on IUD use by women with immunosuppression due to cancer treatment. However, the WHO and the CDC state that IUDs can be used safely by these women [51]. Their recommendations are based on studies assessing IUD use among HIV-positive women, which found that pelvic inflammatory disease and contraceptive failure are rare and that no increased risk for overall complications or infection is observed [81–84]. The limited data on use of IUDs by immunosuppressed women with systemic lupus erythematosus have been reassuring with regards to infection risk. However, the sparse data on use of IUDs by immunosuppressed women who have undergone renal transplant are limited to four case reports with inconsistent results including beneficial effects [85], concerns of infection [86] and contraceptive failure [87]. Thus, further study is needed of the use of IUDs by women with immunosuppression or undergoing chemotherapy.

Radiation to the chest

Women who have been treated with radiation to the chest (e.g., "mantle field" radiation, which was previously a common treatment for Hodgkin's lymphoma) have an increased risk of developing breast cancer [88–91] and thus may want to avoid the potential risks of exogenous estrogen or progestin. However, some clinicians may consider use of modern combined hormonal contraceptives containing low doses of estrogen or use of progestin-only contraceptives acceptable for women who have received chest wall radiation because these methods have not been associated with an increased risk of breast cancer. Nonetheless, the copper T380A IUD is considered the first choice among reversible contraceptives for women who have received chest wall radiation, with the levonorgestrel-containing IUS, which produces the lowest serum hormone levels [92,93], as the second choice.

5. Do contraceptives affect women's risk of developing cancer?

Concerns that oral contraceptives may increase risk of breast cancer are based on a 1996 collaborative reanalysis of 54 studies that found that women who were generally taking older combined hormonal contraceptives containing higher doses of estrogen (or who had used such oral contraceptives in the prior 10 years) had a relative risk of breast cancer of 1.24 (95% CI 1.15–1.33) [94]. However, three recent studies found no association between use of modern oral contraceptives and an increase risk of breast cancer development [95–97]. Furthermore, previous oral contraceptive use has not been shown to effect either all-cause or breast-cancer-specific mortality among women with invasive breast cancer [98,99].

In the general population, the levonorgestrel IUS has not been shown to increase the risk of breast cancer [40,41]. Similarly, use of injectable and implantable progestin-only contraceptives [37,39] has not been associated with an increased risk of breast cancer.

Although ovarian and endometrial cancers are hormonally mediated, the use of progestin-containing contraceptives (whether or not they contain estrogen) actually reduces the risk of these cancers [97–103]. Similarly, use of either the copper T380A IUD or the levonorgestrel IUS appears to reduce risk of endometrial cancer [104,105]. However, findings on whether the levonorgestrel IUS affects the risk of ovarian cancer are inconsistent [106–109], and when ovarian cancer is a concern (e.g., for women who are BRCA1 and BRCA2 carriers) [110,111], systemic levels of progestin that suppress ovulation are preferable to intrauterine or barrier methods of contraception.

6. Is emergency contraception safe for women with cancer?

There are no studies in the current body of literature to address the use of the emergency contraceptive pill in women with cancer or who have undergone cancer therapy. The CDC postulates that emergency contraceptive pills have fewer clinical repercussions than combined oral contraceptives or progestin-only contraceptives as the duration of use is shorter. However, it is unknown how frequent repeated use of emergency contraceptive pills would affect women with cancer who may be advised to avoid other hormonal contraceptive methods. Certainly, use of the copper T380A IUD is safe and effective for both emergency contraception and continued use for birth control in these women.

Conclusions and recommendations

All women seeking contraception should be provided with information about the relative effectiveness of available contraceptives with typical use. For most women who are being treated for cancer, highly effective reversible contraceptives, such as intrauterine or implantable contraceptives, are recommended. For women who have been cancer-free for at least 6 months and have no history of hormonally mediated cancers, chest wall irradiation, anemia, osteoporosis or VTE, the use of any method of contraception can be recommended.

The following recommendations are based on good and consistent scientific evidence (Level A):

- Combined hormonal contraceptive methods (containing estrogen and progestin) should be avoided by women with active cancer or who have been treated for cancer in the last 6 months due to the increased risk of VTE.
- For women with a history of breast cancer, the copper T380A IUD, a highly effective, hormone-free method, is recommended.
- For women with anemia, the levonorgestrel-containing IUS may be used to minimize menstrual blood loss.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- For women with breast cancer treated with tamoxifen, the levonorgestrel-containing IUS provides highly effective contraception and reduces tamoxifen-induced endometrial changes without increasing the risk of breast cancer recurrence.
- For women with a history of chest wall irradiation, systemic estrogen and progestin should be avoided.
- Women with osteopenia or osteoporosis should avoid injectable progestin-only contraceptives.
- Estrogen-containing contraception may be beneficial to women with osteopenia or osteoporosis.
- Women with immunosuppression may safely use intrauterine contraception.
- Emergency contraceptive pills may be used by women at risk of breast cancer or breast cancer recurrence who decline emergency placement of a copper T380A IUD.

Important questions to be answered

Further study of a number of issues would be useful to clinicians providing contraceptive care to women with a history of cancer. In particular, there is a need for well-designed studies with sufficient statistical power to evaluate risks of VTE when progestin-only contraceptives are used by women at high risk of VTE. More data are needed on the effect of the levonorgestrel-containing IUS on breast cancer recurrence risk and the effects of hormonal contraception on risk of breast cancer among women who have received chest wall radiation. Finally, studies of the effect of progestin-only contraceptives on risk of fracture among cancer survivors or, more generally, women with osteopenia and studies of the safety and effectiveness of IUS use by women with immunosuppression would be useful.

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Sources

PUBMED and Google Scholar were searched in English for publications regarding contraception and cancer. In addition, reference lists of identified manuscripts were searched for any additional studies that might be relevant. We also searched the Cochrane Clinical Register of Controlled Trials and clinicaltrials.gov, although randomized trials in this area are challenging to perform.

Authorship

These guidelines were prepared by Ashlesha Patel, MD, MPH; E. Bimla Schwarz, MD, MS, with assistance from Mini Sreedevi, MD, and Alicia Roston, MPH; and were reviewed by the Board of the Society of Family Planning.

Conflict of interest

Ashlesha Patel, MD, MPH; Mini Sreedevi, MD; E. Bimla Schwarz, MD, MS; and Alicia Roston, MPH, report no significant relationship with industry relative to these guidelines. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries.

Intended audience

This Society of Family Planning guideline was developed for its members and other clinicians. This guideline may be of interest to other professional groups that set practice standards for family planning services. The purpose of this document is to review the medical literature regarding cancer and contraception. This evidence-based review should help to guide clinicians providing this care, but it is not intended to dictate clinical care.