Recent Advances in Fertility Preservation and Counseling for Reproductive-Aged Women with Colorectal Cancer: A Systematic Review

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BACKGROUND: The incidence of colorectal cancer among reproductive-aged women is increasing. Concerns regarding future fertility are secondary only to concerns regarding survival and may significantly impact quality of life among reproductive-aged female cancer survivors. Fertility preservation counseling reduces long-term regret and dissatisfaction among cancer survivors. Health care providers counseling patients with colorectal cancer must understand the impact of cancer treatment on future reproductive potential.

OBJECTIVE: This review aims to examine the effects that colorectal cancer treatments have on female fertility and summarize existing and emerging options for fertility preservation.

DATA SOURCES: EMBASE, National Library of Medicine (MEDLINE)/PubMed, Cochrane Review Library were the data sources for this review.

STUDY SELECTION: A systematic literature review was performed using exploded MeSH terms to identify articles examining the effect of surgery, chemotherapy, and radiation, as well as fertility preservation options for colorectal cancer on female fertility. Relevant studies were included.

MAIN OUTCOME MEASURES: The primary outcome was the effect of colorectal cancer treatment on fertility.

RESULTS: There are limited data regarding the impact of colorectal surgery on fertility. The gonadotoxic effects of chemotherapy on reproductive capacity depend on age at the time of chemotherapy administration, cumulative chemotherapy, radiation dose, type of agent, and baseline fertility status. Chemotherapy-induced risks for colorectal cancers are considered low to moderate, whereas pelvic radiation with a dose of 45 to 50 Gray induces premature menopause in greater than 90% of patients. Ovarian transposition may reduce but not eliminate the damaging effect of radiation on the ovaries. Embryo and oocyte cryopreservation are considered standard of care for women desiring fertility preservation, with oocyte cryopreservation no longer being considered experimental. Ovarian tissue cryopreservation remains experimental but may be an option for select patients. The use of gonadotropin-releasing hormone agonists remains controversial and has not been definitively shown to preserve fertility.

LIMITATIONS: The limitations of this review are the lack of randomized controlled trials and high-quality studies, as well as the small sample sizes and the use of surrogate fertility markers.

CONCLUSION: Reproductive-aged women with colorectal cancer benefit from fertility preservation counseling before the initiation of cancer treatment.

KEY WORDS: Chemotherapy; Colectomy; Colorectal cancer/neoplasm; Embryo cryopreservation; Fertility; Fertility preservation; Infertility; Oncofertility; Oocyte cryopreservation; Ovarian tissue cryopreservation; Ovarian transposition; Pelvic radiation.

It is estimated that 67,100 women will be diagnosed with colorectal cancer (CRC) in 2019,[1] making it the third most common cancer diagnosed in women annually. Although the incidence of CRC overall is decreas-

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ing because of increased screening and surveillance, the data from 2005 to 2014 indicate that the incidence among those younger than 55 years of age is increasing.[1] The Surveillance, Epidemiology, and End Results Registry demonstrates a 51% increase in CRC since 1994 in those aged 20 to 49, with 6650 women younger than 50 diagnosed with CRC in 2017.[2] Younger patients with CRC commonly present with more advanced disease at diagnosis.[3] Fortunately, the 5-year survival rate from CRC is improving, with nearly 65% of those diagnosed with CRC surviving at least 5 years from diagnosis.[4]

As survival rates improve, there is an increased focus on the complex issues surrounding cancer survivorship, in particular, for younger women of reproductive age. Among young women diagnosed with cancer, concerns regarding future fertility are secondary only to concerns regarding survival.[5,6] One study found that, among childless cancer survivors, over 75% endorsed wanting children in the future, yet only 6% had undergone infertility treatment.[7] Another study found that among those with GI cancers, including colorectal, over half desired a(nother) child after treatment.[8] Guidelines from the American Society of Clinical Oncology and American Society for Reproductive Medicine state that health care providers should discuss the possibility of infertility and fertility preservation options with all reproductive-age patients diagnosed with cancer.[9,10] Although the majority of men diagnosed with cancer receive information regarding treatment impact on fertility, 40% to 62% of reproductive-age women diagnosed with cancer have reported not receiving fertility counseling at diagnosis or report unmet fertility needs.[11–14] For individuals with newly diagnosed CRC, a fertility discussion was documented with only 33.9% of patients.[15] One qualitative study exploring survivor preference surrounding fertility concerns asked women how they would like to learn about fertility issues; one identified theme was that survivors wanted their doctors or another health care provider to initiate a discussion about their options.[16] Unaddressed fertility concerns may significantly impact quality of life among reproductive-aged female cancer survivors.[12] Receipt of counseling regarding fertility preservation has been shown to reduce long-term regret and dissatisfaction among cancer survivors, and may be associated with both improved physical and psychological quality of life.[8,17,18]

Treatment for CRC often includes a mix of surgery, radiation therapy, and chemotherapy.[19] Various treatment modalities appear to have a differential effect on fertility.[20] Other factors, such as age at the time of cancer treatment, cumulative chemotherapy or radiation dosing, and the individual's baseline fertility status, will affect future reproductive capacity. It is essential that health care providers counseling patients with CRC have an understanding of the impact of cancer treatment on future reproductive potential. This article aims to examine the effects of various treatments for CRC on female fertility and to summarize existing and emerging options for fertility preservation.

MATERIALS AND METHODS

A systematic review of the literature was performed to identify articles examining the effect surgery, chemotherapy, and radiation, as well as fertility preservation options, for CRC on female fertility. Literature repositories reviewed included EMBASE, the National Library of Medicine (MEDLINE)/PubMed, and the Cochrane Review Library. Exploding MeSH terms and combinations thereof were used, including: colorectal neoplasms, colorectal surgery, colectomy, laparoscopy, chemotherapy, radiation, fertility, fertility preservation, infertility, ovarian transposition, uterine transposition, oocyte cryopreservation, ovarian reserve testing, embryo preservation, gonadotropin-releasing hormone, pregnancy, and birth outcomes. Citations from the articles found through search terms were examined for additional relevant articles.

The search was limited to the English language. Included studies were limited to those involving primary data collection (randomized-controlled trials, cohort studies, case-control studies, case series or reports) or review articles (systematic reviews, meta-analyses).

RESULTS

Counseling

When caring for a reproductive-aged female patient with a new diagnosis of CRC, a multidisciplinary approach is ideal to balance both the need for urgent initiation of treatment and the patient's potential desire for future fertility. Gamete cryopreservation is the first-line approach for fertility preservation; however, it necessitates an approximate 2-week delay in initiation of cancer therapy. Oocyte and embryo cryopreservation are not recommended during chemotherapy because of the low yield of oocytes and the potential increased risk of birth defects.[21,22]

Before the initiation of cancer therapy, obtaining a baseline fertility evaluation may be useful. Ovarian reserve is best measured in this population via anti-Müllerian hormone (AMH) testing. AMH is a glycoprotein product of small antral and preantral follicles and estimates an individual's ovarian reserve.[23,24] Anti-Müllerian hormone may also be utilized as a marker of ovarian recovery following the insult of gonadotoxic agents.[24,25] Individuals with higher pretreatment AMH values may be more likely to regain ovarian function following cancer treatment.[25–28] An AMH greater than 1.0 ng/mL in an adult female patient indicates good ovarian reserve, whereas values less than 1.0 ng/mL suggest a suboptimal ovarian reserve.

There is scant research on pregnancy outcomes, particularly in those specifically with CRC. However, multiple

successful pregnancies following treatment for CRC have been reported.[29–31] In those who are able to conceive, birth outcomes after cancer treatment are reassuring overall. Those who have been exposed to pelvic radiation may be at an increased risk for pregnancy complications, including preterm birth and low-birth-weight babies.[32] There does not appear to be an increased risk of cancer recurrence in those who receive fertility medication before, during, or after their cancer treatment,[33,34] although long-term data are limited. Patients are often counseled to wait at least 2 years following cancer diagnosis to attempt conception, because 80% of CRC recurrences will occur within the first 2 years of diagnosis and treatment.[35]

For those unable to conceive with their own gametes, third-party reproductive options, such as oocyte donation, embryo adoption, gestational surrogacy, or child adoption, should be offered. Over 60% of cancer survivors may be willing to adopt if they cannot have a biological child.[7] Counseling should be offered to address the potential psychosocial impact associated with the loss of fertility.

Impact of Colorectal Cancer Treatments on Fertility

Surgery

There are exceedingly limited data regarding the fertility impact of colorectal surgery. Utilizing the existing data regarding surgical management of other colorectal conditions, such as inflammatory bowel disease (IBD) or familial adenomatous polyposis, may be helpful. Total proctocolectomy with ileal pouch-anal anastamosis (IPAA) has previously been shown to be associated with postsurgical infertility.[36–38] A review of patients over a 30-year time span between 1980 and 2010 found that women with ulcerative colitis (UC) who did not undergo IPAA had higher birth rates (46.8 children/1000 years) than those who underwent IPAA (27.6 children/1000 years).[39] Additional studies have explored fertility outcomes comparing handsewn versus stapled IPAA; although not significant, there was a trend for improved female fertility in those who had handsewn anastomoses.[40] Advances in minimally invasive surgery may be beneficial for individuals with CRC who are concerned about their fertility. In a limited series of 15 patients attempting to conceive after laparoscopic IPAA, 73% had successful live births.[41] A potential explanation for preserved fertility in those undergoing laparoscopic IPAA may be decreased chance of postsurgical adhesion formation following a laparoscopic versus open approach.[42]

More recent studies have also explored the effect of surgery on in vitro fertilization success. A 2015 study demonstrated that those with UC who had undergone IPAA achieved live birth rates similar to those with UC who did not undergo IPAA; live birth rates were also similar to women without IBD.[43] However, a recent Danish study followed women with UC, women with Crohn's disease (CD), and women without IBD receiving first-time assisted-reproductive technology treatment. The adjusted odds ratio (OR) of a live birth was 0.82 (95% CI, 0.57–1.17) for women with UC and 0.58 (95% CI, 0.32–1.03) for women with CD in comparison with women without IBD.[44] In those with CD who had previously undergone surgery versus no surgery, the adjusted OR of a live birth was significantly decreased (0.29; 95% CI, 0.13–0.65); an appreciable difference was not similarly noted in women with UC who had undergone surgery versus those who had not undergone surgery (adjusted OR, 0.81; 95% CI, 0.47–1.40).[44] Additional research is needed to assess the effects that open surgery versus laparoscopic surgery may have on fertility in those undergoing colorectal surgery for colon cancer.

Chemotherapy and Radiation

The gonadotoxic effects of chemotherapy on reproductive capacity depend on the age at the time of chemotherapy administration, cumulative chemotherapy and radiation dose, the type of agent, as well as a baseline fertility status of the individual. Chemotherapeutic agents with high gonadal toxic risks include cyclophosphamide, ifosfamide, melphalan B sulfate, nitrogen mustard, procarbazine, and chlorambucil (Table 1).[45,46] Cisplatin and oxaliplatin have moderate gonadotoxic toxic effects.[45] 5-Fluorouracil, methotrexate, actinomycin D, bleomycin, and vincristine have mild or minimal toxic potential.[45] Cercek et al[47] reported that 16% of women under age 50 experienced persistent amenorrhea following the administration of FOLFOX6. However this study was not powered sufficiently to ascertain the difference in amenorrhea rates between women younger than 40 and women between 40 and 50. The largest fertility study to date among CRC survivors evaluated 123 premenopausal women age 40 and younger.[45] Only 4.2% (3/72) of this study population with colon cancer experienced persistent amenorrhea, yet 94.1% (48/51) of patients with rectal cancer experienced persistent amenorrhea ($p < 0.01$).[45]

TABLE 1. Chemotherapeutic agents for colorectal cancer and their relative gonadotoxicities

High toxicity
Cyclophosphamide
Ifosfamide
Melphalan B sulfate
Nitrogen mustard
Procarbazine
Chlorambucil
Moderate toxicity
Cisplatin
Oxaliplatin
Mild or minimal toxicity
5-Fluorouracil
Methotrexate
Actinomycin D
Bleomycin
Vincristine

Sources: Wan et al[45] and Dolmans.[85]

According to summary guidelines from the *Ferti*PROTEKT Network, a network and society of physicians and biologists specializing in fertility preservation, chemotherapy-induced risks for colorectal cancers are considered low to moderate, but high if pelvic radiation is performed.[48] A radiotherapy dose of 45 to 50 Gray (Gy) induces premature menopause in more than 90% of patients with rectal cancer.[48] It is difficult, however, to predict the effect chemotherapy has on fertility, with 1 documented case of ovarian failure developing following 5-fluorouracil therapy for CRC.[49]

Antiangiogenic agents such as bevacizumab have an unknown impact on long-term fertility. In 2011 the Food and Drug Administration required the addition of a revised package insert warning of potential unfavorable fertility effects in light of a study involving 179 patients with colon cancer exposed to bevacizumab.[50] Those utilizing bevacizumab + FOLFOX experienced a 34% ovarian failure rate compared with 2% that did not utilize bevacizumab.[51] Ovarian function returned in approximately 20% of women after discontinuation of bevacizumab therapy. In contrast, trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor, has not been shown to increase the risk of ovarian failure.[52]

Fertility Preservation Treatment Options

There are many fertility preservation treatment options available for reproductive-aged patients diagnosed with CRC who desire future fertility (Fig. 1).

Ovarian Transposition

One of the surgical options for women undergoing pelvic radiation therapy who desire future fertility is ovarian transposition (oophoropexy). Ovarian transposition involves mobilizing one or both of the ovaries and attaching them to the sidewall of the abdomen at the pelvic brim.[53] This technique is typically used to avoid the damaging effects of radiation on the ovaries. It is estimated that the lethal dose of radiation required to eliminate 50% of oocytes (LD_{50}) is 2 Gy.[54] Because cumulative radiation doses for CRC typically approximate 50 Gy,[55] transposition of the gonads away from the target area is crucial given their radiosensitivity. Ovarian transposition may be performed either open or laparoscopically, although the laparoscopic approach is increasingly preferred because of less postoperative pain, faster recovery, and shorter hospital stay.[53,56] Even with oophoropexy, the ovaries are not without risk of damage, because they can still receive 8% to 15% of the prescribed dose of radiation due to scatter and transmission through a pelvic shield.[57,58]

There are various surgical approaches for oophoropexy. The classic approach involves transection of the utero-ovarian ligament with transposition of the ovaries laterally and anteriorly at the level of the anterosuperior iliac spines,[53,54,59] often anchoring to the peritoneum with radiopaque clips to facilitate future visualization (Fig. 2).[53,57,59–63] The ovarian blood supply in the infundibulopelvic ligament is isolated and mobilized away from the

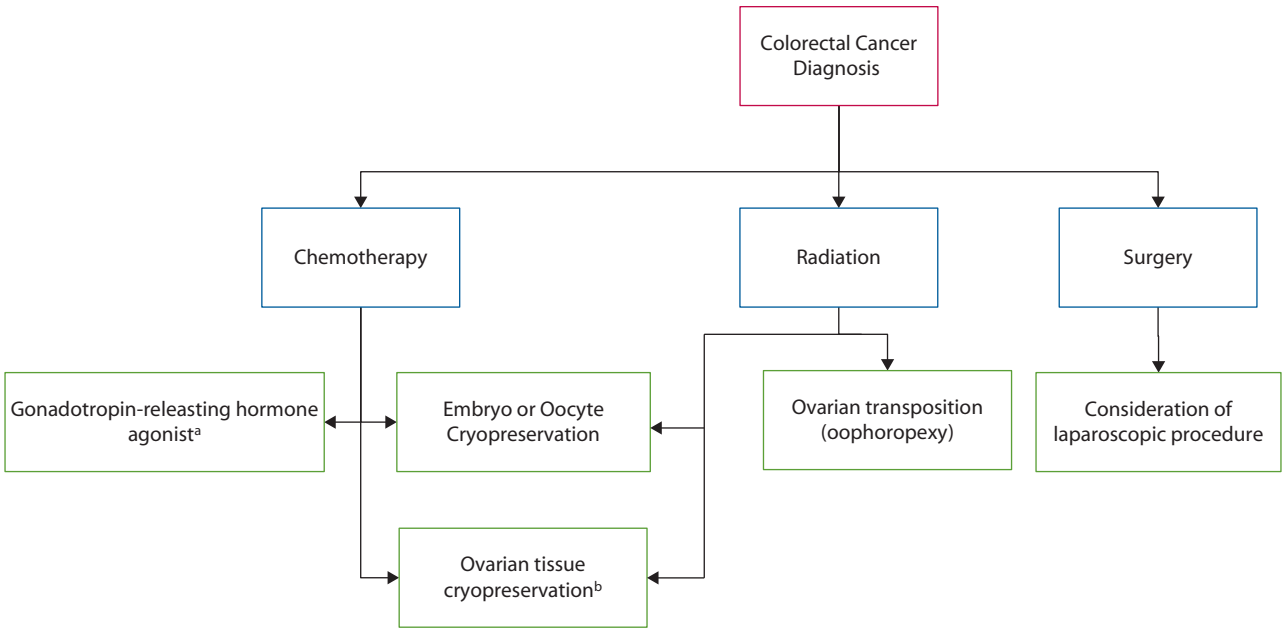

FIGURE 1. Fertility preservation options for reproductive-aged women diagnosed with colorectal cancer. [a]The use of gonadotropin-releasing hormone (GnRH) agonists has not been definitively shown to be associated with improvement in fertility outcomes and remains controversial. American Society of Clinical Oncology guidelines recommend that patients be offered GnRH agonist treatment if there is a high likelihood of chemotherapy-induced ovarian failure; however, patients should be extensively counseled regarding the conflicting data of its efficacy, and GnRH agonists should not be used to replace other proven fertility preservation methods. [b]Ovarian tissue cryopreservation is still considered experimental. Use of the Edinburgh criteria may help to identify patients who would be appropriate candidates for ovarian tissue cryopreservation.

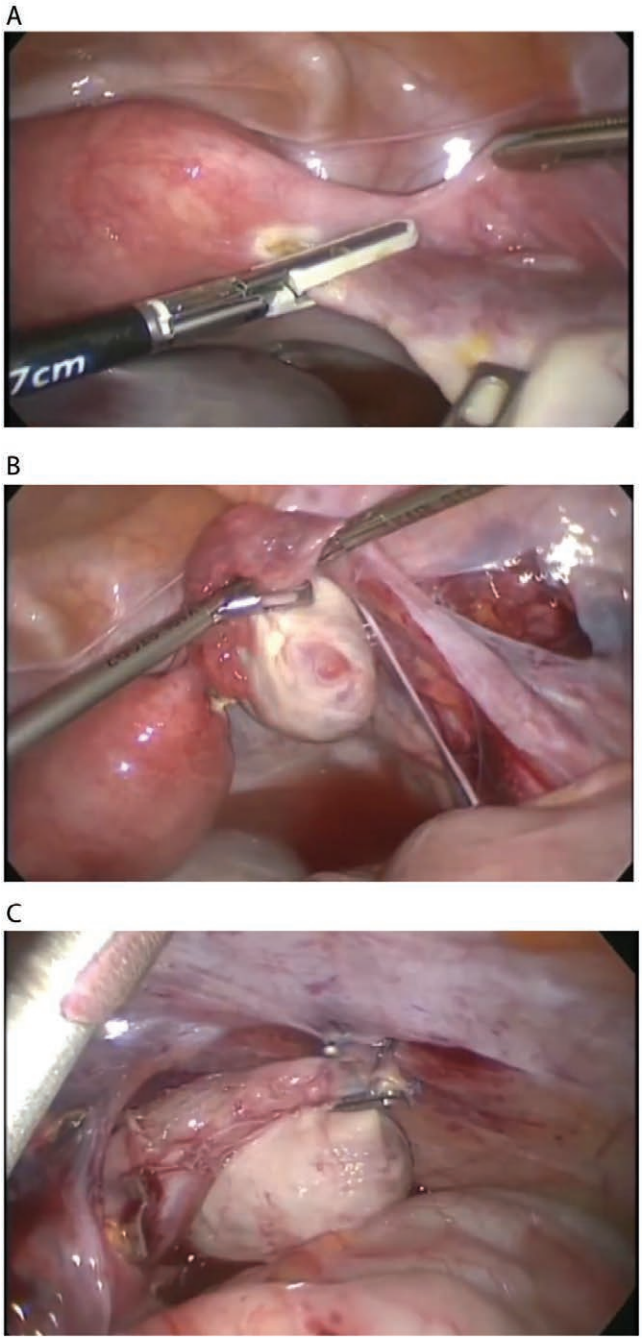

FIGURE 2. Ovarian transposition technique. A, Transection of the utero-ovarian ligament. B, Isolation of the ovarian blood supply both medially and laterally to the infundibulopelvic ligament. C, Mobilization of the ovary through a retroperitoneal tunnel toward the pelvic brim where it is then secured and anchored to the peritoneum above the iliac crest and tagged with surgical clips for ease of identification on future imaging. Reproduced from: Arian SE, Goodman L, Flyckt RL, Falcone T. Ovarian transposition: a surgical option for fertility preservation. *Fertil Steril*. 2017;107:e15,[53] with permission from Elsevier.

ureter by incising the peritoneum medially and laterally to the infundibulopelvic ligament.[53,58,62] Once the ovary has been mobilized, it can be guided through a retroperitoneal tunnel toward the pelvic brim where it is then secured and anchored to the peritoneum above the iliac crest at the abdominal sidewall.[53,57–59,62]

Methods to assess the success of oophoropexy vary. Scant data exist regarding pregnancy rates in those attempting pregnancy after oophoropexy and subsequent pelvic radiotherapy for CRC. A series of 11 women who underwent oophoropexy before radiotherapy for Hodgkin lymphoma reported 14 pregnancies among the 11 women, with 12 live births.[64] Spontaneous pregnancies following ovarian transposition[30] in patients with CRC have been reported, although the cases are exceedingly limited.[65] Separate meta-analyses have reported that ovarian transposition in women younger than 40 years is associated with an 70% to 88.6% chance of fertility preservation.[66,67] However, one meta-analysis assessed ovarian function by a combination of hormonal levels and menses,[66] and the other assessed ovarian function by a combination of hormonal levels and morphological appearance of follicles on ultrasound.[67]

Uterine Transposition and Fixation

Oophoropexy may move the ovaries out of the field of radiation but still leave the uterus vulnerable to the side effects of radiation, such as reduction of uterine volume, endometrial damage or fibrosis, and decrease in vascular perfusion.[68] In some cases of CRC, the uterus may be fixed to the anterior abdominal wall to attempt to spare the uterus from high doses of radiation exposure.[31] One recently suggested fertility-sparing technique is uterine transposition. Uterine transposition involves repositioning the uterus into the upper abdomen to avoid radiation exposure before subsequently repositioning it in the pelvis following treatment.[68,69] This surgery can be done laparoscopically and involves transecting the round ligament at the pelvic sidewall, separating the broad ligament, ligating the uterine arteries, and making a colpotomy ring to separate the cervix from the vagina.[68,69] The uterus is transposed to the upper abdomen and fixed to the anterior abdominal wall, fixing the cervix to the fascia near an umbilical incision.[69] Although the technique for uterine transposition has been demonstrated, it is considered experimental, and data regarding subsequent pregnancy outcomes do not exist.

Oocyte and Embryo Cryopreservation

Although oophoropexy may be able to attenuate radiation-induced gonadotoxicity, it will not protect the ovaries from the potential gonadotoxicity of chemotherapy. Consequently, it is advisable for select patients to consider oocyte or embryo cryopreservation before the initiation of treatment for CRC. Oocyte and embryo cryopreservation involve hormonal stimulation of the ovaries and conventionally require 2 to 4 weeks to undergo 1 cryopreservation attempt.[70] Ovarian stimulation was typically initiated at the onset of menses, although more recent stimulation protocols start immediately. The advantage of "random

start" ovarian stimulation is the timeframe to oocyte retrieval is shortened and avoids further delay in initiation of chemotherapy.[70] Random start protocols produce a similar number of mature oocytes as conventional ovarian stimulation protocols.[71]

Embryo cryopreservation requires a male partner or sperm donor at the time of oocyte harvest. For women who do not have a partner, do not wish to utilize donated sperm, or who have an ethical or religious objection to embryo freezing, oocyte cryopreservation is an option.[10] As of 2012, American Society for Reproductive Medicine no longer deemed oocyte cryopreservation experimental.[10,72,73] Evaluation of more than 900 births resulting from oocyte cryopreservation demonstrated no greater risk of congenital anomalies compared with spontaneous conception.[74] Oocyte cryopreservation involves a similar stimulation protocol used for embryo cryopreservation. However, rather than performing fertilization of the oocytes and cryopreservation of subsequent embryos, the oocytes are cryopreserved unfertilized. Fresh and frozen oocytes yield similar pregnancy rates in subsequent in vitro fertilization cycles, with clinical pregnancy rates ranging from 36% to 65%.[72,75,76]

Methods for gamete cryopreservation continue to improve. Traditionally, oocytes and embryos have been cryopreserved utilizing a slow-freeze technique. While resulting in high embryo survival rates, oocyte survival rates were suboptimal secondary to the formation of intracellular ice crystals.[77] Current cryopreservation techniques utilize vitrification, which induces a rapid phase change and improved oocyte survival. Vitrification was found to be associated with increased ongoing clinical pregnancy rate per cycle (relative risk ratio [RR], 2.81; 95% CI, 1.05–7.51) compared with slow-freeze cryopreservation techniques.[75] A meta-analysis from 7 randomized-controlled trials comparing vitrification versus slow freezing for embryo cryopreservation showed improved embryo survival with vitrification (RR, 1.59; 95% CI, 1.30–1.93) and higher clinical pregnancy rates (RR, 1.89; 95% CI, 1.00–3.59).[75] Collectively, these data suggest that vitrification/warming is superior to slow freezing/thawing with regard to gamete survival and clinical pregnancy rates for both embryos and oocytes. Gamete cryopreservation is now considered standard of care for women desiring fertility preservation.

Ovarian Tissue Cryopreservation

Despite the current use of random start protocols, women diagnosed with CRC who wish to preserve their fertility through embryo or oocyte cryopreservation will still require a 2-week timeframe for fertility preservation. Ovarian tissue cryopreservation may be an option for women who must undergo urgent chemotherapy initiation; however, this method of fertility preservation is still considered experimental.[78] Ovarian tissue cryopreservation requires laparoscopic removal of a portion, one, or both ovaries, which are then sectioned into strips of tissue less than 2 mm thick and cryopreserved.[79,80] The ovarian tissue is then subsequently autotransplanted to the patient following completion of treatment with gonadotoxic agents. Transplantation may be performed in an orthotopic manner by reintroduction into the pelvis[79] or a heterotopic (extrapelvic) manner with transplantation to the forearm or abdominal wall.[81] Resumption of ovarian tissue function has been documented, resulting in both pregnancy[79,82] and return of endogenous hormone production.[79,82,83]

The Edinburgh criteria (Table 2) identify potentially appropriate candidates for ovarian tissue cryopreservation.[84] Candidates include those younger than 30 years who have had no previous chemotherapy or radiation; who have a realistic chance of long-term survival and high risk of treatment-induced immediate ovarian failure; who are able to given informed consent; are HIV, hepatitis, and syphilis negative; and who have no existing children.[84,85] These guidelines are based on multidisciplinary discussion.[84,85]

At the time of this writing, just over 130 births have been documented from ovarian tissue cryopreservation and reimplantation.[46,86,87] Ovarian tissue transplantation restored endocrine function in 85.2% (144/169) of patients.[88] Pregnancy success rates range from 23% to 37% in most reports.[89] Of the 77 births and pregnancies where data were available, the majority (62.3%) conceived spontaneously.[88] Case reports exist of young women diagnosed with CRC who underwent ovarian tissue cryopreservation followed by receipt of gonadotoxic chemoradiation.[29,90] In these limited reports, women demonstrated return of regular menses, growth of ovarian follicles, normalization of serum hormone measurements to premenopausal levels, and subsequent pregnancy.[82,90–92] Despite promising results thus far, additional research is needed regarding ovarian tissue cryopreservation to optimize protocols.

A significant concern regarding ovarian tissue transplantation in oncology patients is the risk of reimplantation of malignant cells.[93] In patients with leukemia, ovarian tissue transplantation is not recommended because a significant percentage of harvested ovarian tissue demonstrates leukemic cells.[10] In CRC specifically, data

TABLE 2. Edinburgh criteria for the determination of appropriate candidates for ovarian tissue cryopreservation

Younger than 30 years
Has had no previous chemotherapy or radiation (patients <15 years with exposure to previous low-risk chemotherapy can also be considered)
Has a realistic chance of long-term survival (>5 years)
Has a high risk of immediate treatment-induced ovarian failure (estimated risk >50%)
Able to give informed consent
Negative HIV, hepatitis, and syphilis serology
Has no existing children

Sources: Wallace et al[84] and Dolmans.[85]

are sparse. One report described a patient with anal cancer who underwent ovarian tissue cryopreservation and transplantation; no malignant cells were detected on histology in the ovarian tissue graft.[92] However, CRC has been demonstrated to spread to the ovaries in autopsy studies, with 1 study reporting a frequency between 16.7% and 31.1% of specimens.[94,95] Ovarian metastases have also been found in patients with appendiceal cancer in 28.6% of cases.[96] Metastases to the ovary have been found in 5% to 10% of women with metastatic CRC,[97,98] occurring disproportionately in younger women. These tumors often respond poorly to chemotherapy and carry a dismal prognosis.[98] In patients with metastasis to an ovary, bilateral oophorectomy is recommended.[99] Overall, the risk of ovarian metastases appears to be low in CRC stages pT1–3.[48] However, there have been case reports of patients with CRC with negative lymph nodes who are found to have micrometastases in ovaries that appeared otherwise grossly normal.[100] Given the sometimes-unpredictable spread of CRC to the ovaries, the scant data regarding ovarian tissue cryopreservation specifically in patients with CRC, and the experimental nature of ovarian tissue cryopreservation, reimplantation of ovarian tissue in CRC survivors should be approached with caution.

Gonadotropin-Releasing Hormone Agonist

Gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate, are often used as a means of fertility preservation in patients with cancer who are undergoing chemotherapy. Several mechanisms have been proposed by which GnRH agonists may act to be protective of fertility, including follicle-stimulating hormone suppression leading to a decreased number of primordial follicles entering development, hypoestrogenism causing a decrease in ovarian perfusion and therefore lower exposure of the ovaries to cytotoxic chemotherapeutic agents, and a direct effect on the ovary that protects the germline stem cells.[80,101] Despite these proposed mechanisms, GnRH use has not been definitively shown to improve fertility outcomes and remains controversial.[82,102–104] A meta-analysis of 11 randomized-controlled trials with 1062 participants demonstrated a greater number of women treated with a GnRH agonist resuming menses after chemotherapy (pooled OR, 2.57; 95% CI, 1.65–4.01), but subgroup analysis failed to show a difference in spontaneous pregnancy rates between those who did and did not receive GnRH agonist during chemotherapy (pooled OR, 1.77; 95% CI, 0.92–3.40).[105] Most of the research assessing GnRH agonists as protective agents has been performed in women with breast cancer, with no studies evaluating a GnRH agonist in patients with CRC. Consequently, the most recent American Society of Clinical Oncology guidelines from 2018 recommend that patients be offered GnRH agonist treatment if there is high likelihood of chemotherapy-induced ovarian failure; however, patients should be extensively counseled regarding the conflicting data of its efficacy, and GnRH agonists should not be used to replace other proven fertility preservation methods.[10]

CONCLUSION

Reproductive-aged women with a new diagnosis of CRC should be counseled regarding the potential fertility impact of their specific treatment regimen. The majority of patients with CRC undergoing radiation therapy will experience ovarian failure. Obtaining a baseline fertility assessment and discussing the range of future family-building options is recommended. Ovarian suppression with GnRH agonists is controversial in regard to gonadal protection and should not be utilized as a first-line intervention. Oocyte cryopreservation is no longer considered experimental, and success rates are encouraging with the use of vitrification as the cryopreservation method. Ovarian tissue cryopreservation is still considered experimental; however, as techniques continue to improve, it may become the future standard of care. Oncofertility encompasses a multidisciplinary approach in the care of reproductive-aged patients with cancer, providing the best opportunity for future reproductive success.

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