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Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine Evidence-Based Review

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Abstract: Providers who care for women at risk for hereditary gynecologic cancers must consider the impact of these conditions on reproductive and hormonal health. This document reviews potential options for cancer prevention, family building, genetic testing and management of surgical menopause in this patient population. (Fertil Steril® 2019;112:1034–42. ©2019 by American Society for Reproductive Medicine.)

Keywords: Genetic counseling, ovarian cancer, endometrial cancer, quality of life issues, menopause and hormone replacement therapy

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Highlights

- Women at risk for hereditary gynecologic cancers have unique concerns regarding fertility and hormonal health.
- There are multiple fertility preservation strategies that can be used to help women achieve their procreative goals.
- Genetic testing can be used before embryo transfer to identify whether an embryo carries a pathogenic gene variant.
- For women with who don't have a personal history of breast cancer, hormone therapy can be considered.

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1. INTRODUCTION

Approximately 5–10% of all cancers can be attributed to hereditary cancer syndromes. Recognition of these conditions facilitates the ability to screen and identify individuals at increased risk and intervene for those found to carry pathogenic gene variants. Identification and intervention have consequences beyond the obvious goals of cancer prevention and early detection. There can also be an impact on reproductive choices, decisions about fertility, family building and hormonal status.

Inherited pathogenic variants that are associated with gynecologic cancers are particularly unique because they may require interventions that interrupt normal reproductive function including hormone production and fertility. Some pathogenic variants also increase the risk of other cancers such as breast cancer, for which treatment (particularly chemotherapy or oophorectomy) may also negatively impact reproductive function. Women who are carriers of a hereditary pathogenic gene variant that increases their risk for gynecologic cancer should be counseled on strategies for cancer prevention, their future fertility, risk of transmitting pathogenic gene variants to their offspring, and the potential use of hormone therapy (HT) after risk-reducing oophorectomy. An understanding of cancer risk and the preventive strategies that are used to mitigate this risk can help reproductive specialists counsel affected women on topics such as timing of fertility preservation and the availability of preimplantation genetic testing. Similarly, an understanding of the logistics of assisted reproductive technology (ART) can assist gynecologic oncologists in treatment planning and facilitate early referral to reproductive specialists to ensure that a woman's fertility concerns are met in a timely fashion. The purpose of this document is to highlight the reproductive and hormonal consequences that women who are at high risk of developing a gynecologic cancer face, and to unite efforts of gynecologic oncologists and reproductive medicine specialists in providing and optimizing care of this unique population.

2. GENETIC CONDITIONS ASSOCIATED WITH GYNECOLOGIC CANCERS

The most common conditions associated with gynecologic cancers include Hereditary Breast and Ovarian Cancer (HBOC) and Lynch (Hereditary Nonpolyposis Colorectal Cancer or HNPCC) syndromes. Both are inherited in an autosomal dominant pattern. HBOC is characterized by pathogenic variants in tumor suppressor genes (1) that increase the risk of breast, ovarian, pancreatic, and prostate cancer. Approximately 5% of breast cancers and 10% to 25% of ovarian cancers are due to HBOC. The risk of developing ovarian cancer by age 70 in BReast CAncer gene 1 (*BRCA1*) carriers is 39–46% and 10–27% for BReast CAncer gene 2 (*BRCA2)* carriers (2, 3). The risk of ovarian cancer increases after age 40, with up to 20% of women with pathogenic *BRCA1* variants developing ovarian cancer by age 50, compared with 3% of *BRCA2*

TABLE 1

Selected cancer risk gene variants and their impact.

Gene	Risk of ovarian cancer	Risk of breast cancer	Risk of endometrial cancer
ATM	No increase	Increased	No increase
BRCA1	Increased	Increased	No increase
BRCA2	Increased	Increased	No increase
BRIP1	Increased	No increase	No increase
CDH1	No increase	Increased	No increase
CHEK2	No increase	Increased	No increase
Lynch Syndrome Genes: MLH1, MSH2, MSH6, PMS2, and EpCAM	Increased	Insufficient evidence	Increased
PALB2	No increase	Increased	No increase
PTEN	No increase	Increased	Increased
STK11	Increased	Increased	No increase
RAD51C	Increased	No increase	No increase
RAD51D	Increased	No increase	No increase
TP53	No increase	Increased	No increase

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mutation carriers (1). Additionally, women carrying a germline pathogenic variant in BRIP1 have an 8 to 11-fold increased relative risk (RR) for developing ovarian cancer, without a significantly increased risk for breast cancer. Pathogenic variants in *RAD51C* and *RAD51D* are also associated with an increased risk for ovarian cancer without a significantly increased risk for breast cancer. In contrast, pathogenic variants in *TP53, CDH1, CHEK2*, and *ATM* are associated with an increased risk of breast cancer without a significantly increased risk for ovarian cancer (1). Pathogenic variants in *STK11* are associated with sex-cord stromal ovarian tumors, and variants in *PTEN* are associated with an increased risk of breast and endometrial cancer, but not ovarian cancer.

Lynch Syndrome is associated with pathogenic variants in one of a family of mismatch repair genes (4). Each gene mutation is associated with a different cancer risk profile and distribution of lifetime cancer incidence. Lynch Syndrome is associated with an increased risk of colorectal cancer as well as endometrial, stomach, breast, ovarian, small bowel, pancreatic, prostate, urinary tract, liver, kidney, and bile duct cancers. About 3% to 5% of all cases of colorectal cancer and 2% to 3% of all cases of endometrial cancer are thought to be due to Lynch Syndrome (4, 5). The Lynch genes vary in penetrance, with a lifetime risk of up to 60% for endometrial and up to 24% for ovarian cancer (5), depending on the gene. (See Table 1).

3. SURVEILLANCE, CHEMOPREVENTION, AND RISK–REDUCING SURGERY FOR GYNECOLOGIC CANCERS

To reduce gynecologic cancer risk, women may opt for surgeries such as risk-reducing bilateral salpingo-oophorectomy (RRSO), bilateral salpingectomy or hysterectomy. Because hereditary cancers are associated with a relatively younger age of onset, risk-reducing surgeries are generally recommended between the ages of 35–45, or when childbearing is complete. These risk-reducing procedures may result in premature menopause and infertility, consequences which significantly impact general health status and quality of life.

3.1. Women at Highest Risk for Hereditary Ovarian Cancer

3.1.1. Surveillance. To date, there are no effective screening tests for early identification of ovarian cancer, even in high-risk *BRCA1 and BRCA2* mutation carrier populations. Screening by CA-125 and transvaginal ultrasound may be an option for high risk women who elect to defer or decline risk-reducing salpingo-oophorectomy (6). Cancer detected through high risk screening programs may be detected at a point of lower clinical disease burden, although the impact of diagnosis at earlier stage on survival remains unclear (7).

3.1.2. Chemoprevention. Several classes of drugs, including oral contraceptives (OCPs), non-steroidal anti-inflammatory drugs, retinoids, angiopreventive agents, poly(ADP-ribose) polymerase (PARP) inhibitors, and tyrosine kinase inhibitors have been investigated for chemoprevention of ovarian cancer. However, the data are not conclusive except for OCPs. Oral contraceptive pills have been shown to reduce the risk of ovarian cancer by approximately half in women at average risk for ovarian cancer (8) as well as in women who carry pathogenic variants in *BRCA1 and BRCA2* (summary relative risk [SRR], 0.50; 95% CI, 0.33–0.75) (9). The protective benefit of OCPS increases with duration of use. However, the safety of OCP use with regard to the development of breast cancer in *BRCA* mutation carriers is not entirely clear. While OCP use has been shown in some studies to be associated with a small increase in risk of breast cancer in the general population (10, 11), this was not demonstrated in case control studies of women who carry *BRCA1 and BRCA2* mutations (9); however, cohort studies showed an increased risk of breast cancer for women with *BRCA1* mutations (ES = 1.59; 95% CI = 1.32 to 1.92) and women with *BRCA2* mutations (ES = 1.85; 95% CI = 1.30 to

2.64) who had used OCPs (10). OCPs can be used to reduce the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers without a personal history of breast cancer (11), with the understanding that the impact on breast cancer risk is indeterminate. Further studies are needed to determine the optimal timing for administration of OCPS and quantify actual breast cancer risk.

3.1.3. Risk-reducing surgery

3.1.3.1. Risk-reducing Salpingo-oophorectomy (RRSO). RRSO is the most effective method for reducing the risk of ovarian cancer in high-risk women, with reported reductions in incidence of up to 70–85% (12, 13). In addition to decreased ovarian cancer mortality, RRSO has been associated with reductions in breast cancer mortality and all-cause mortality in this population, and is recommended on completion of childbearing, between the ages of 35–40 for *BRCA1* mutation carriers, and between the ages of 40–45 for *BRCA2* mutation carriers (14). This reduction in all-cause mortality with RRSO in *BRCA1 and BRCA2* mutation carriers contrasts with the findings in the general population, where ovarian conservation is reported to significantly lower the hazard of all-cause mortality (13, 15).

Occult underlying ovarian cancers have been identified in pathology specimens from RRSO procedures (16, 17). Given the risk of occult malignancy, pathologists should section the ovaries and fallopian tubes serially at two-millimeter intervals using the "Sectioning and Extensively Examining the Fimbriated End" (SEE-FIM) protocol (17). As the distal fallopian tube is the dominant site for the origin for early malignancies in women undergoing RRSO, salpingectomy is essential for optimal risk-reduction (18). Up to 10% of women will have neoplasia (pre-cancers and cancers) on pathology at time of RRSO and are at risk of recurrent disease.

Women considering RRSO should be informed about the common sequelae of surgical menopause, including vasomotor symptoms, osteoporosis, decreased libido, symptoms of vaginal atrophy and cardiovascular disease. Hormone therapy (HT) can prevent and alleviate many of the symptoms associated with surgical menopause (19). Nonhormonal treatment strategies are also available for women who have contraindications to HT. Decisions about whether or not to use HT should be individualized, considering symptom severity and cancer history.

3.1.3.2. Risk reducing salpingectomy. A significant number of women with *BRCA1 and BRCA2* pathogenic variants opt not to pursue RRSO to preserve fertility and/or avoid the development of surgical menopause. It has been proposed that since many high-grade serous cancers originate in the fallopian tube, complete removal of the fallopian tubes and fimbriae may decrease the risk of ovarian cancer. However, there are no data on actual risk reduction and patients should understand that RRSO is the standard of care. Bilateral salpingectomy should be reserved for women who decline RRSO at the recommended age. These women should also be informed that unlike RRSO, bilateral salpingectomy does not decrease breast cancer risk and they should be encouraged to undergo eventual completion bilateral oophorectomy (12).

3.1.3.3. Hysterectomy. The role of hysterectomy in *BRCA* mutation carriers is controversial. In one study, the presence of *BRCA1* mutations was documented in four out of 20 Jewish women with uterine papillary serous carcinoma (UPSC) (20). Studies to date on the association of *BRCA* mutations with UPSC have been small and have reported conflicting results. Although the overall risk of endometrial cancer after risk-reducing salpingo-oophorectomy is low, there seems to be a higher risk of serous and serous-like endometrial cancers in *BRCA1* mutation carrier women, relative to grade 1 endometrioid endometrial cancers (21). Hysterectomy may also be considered to simplify and lower the risk of post-op HT regimens, allowing replacement of estrogen only instead of estrogen and progestin.

3.2. Women at Highest Risk for Hereditary Uterine Cancer

3.2.1. Surveillance. Multiple strategies for endometrial cancer screening have been proposed, including transvaginal ultrasound, endometrial biopsy, a combination of both, office hysteroscopy with biopsy and endometrial washings. Though there is no clear evidence to support screening in women with Lynch Syndrome, the National Comprehensive Cancer Network (NCCN) guidelines state that office endometrial sampling every 1–2 years is a viable option (14).

3.2.2. Chemoprevention. Oral contraceptives have been shown to decrease the risk of endometrial cancer by 50% in the general population (22). It has been shown that the endometrium of women with Lynch Syndrome that are exposed to Depo-Medroxyprogesterone or OCPs for three months show decreased epithelial proliferation and inactive/secretory histology, suggesting that these agents may be useful for chemoprevention of uterine and possibly, ovarian cancer. However, whether these effects result in an actual reduction in the risk of endometrial cancer is unknown (23). The levonorgestrol intrauterine system is also associated with lower endometrial cancer risk and has been used in treating early low-grade disease, but there are limited data for chemoprevention in Lynch Syndrome (24, 25).

3.2.3. Risk reducing surgery. Women with Lynch Syndrome should consider prophylactic total hysterectomy and bilateral salpingo-oophorectomy (THBSO) at the completion of childbearing, especially after the age of 40 years (4). THBSO has been demonstrated to decrease the risk of endometrial and ovarian cancer in this patient population (26). Exact timing should be individualized, based on additional factors including menopause status, comorbidities, and specific gene mutation (5). Prior to THBSO, women should undergo endometrial biopsy to rule out the possibility of an occult cancer. Women should be fully informed of the sequelae of premature menopause.

4. FERTILITY AND FAMILY BUILDING IN WOMEN WITH PATHOGENIC VARIANTS IN HEREDITARY CANCER GENES

4.1. Fertility Preservation

Ideally, women should complete their childbearing prior to definitive surgery. The recommended timing for RRSO occurs

during women's childbearing years (ages 35–45) and may be even sooner, such as in cases where a family member was diagnosed with cancer at a very young age. In these instances, women may experience a narrower window for fertility. While decreasing cancer risk, RRSO prematurely eliminates the possibility of having a future biological child unless a woman has cryopreserved oocytes or embryos through ART. Additionally, *BRCA1 and BRCA2* mutation carriers who have been diagnosed with cancer that requires chemotherapy may be at risk of experiencing treatment-related infertility and premature ovarian insufficiency or menopause. Considering options for fertility preservation (FP) is an important component of care for these women.

Early referral (age late 20s-early 30s) of women with *BRCA1 and BRCA2* pathogenic variants to reproductive endocrinologists is strongly encouraged so that they can be informed of the availability of fertility preservation and the potential for preimplantation genetic testing (PGT). This also facilitates establishment of baseline ovarian reserve and allows women who are interested to pursue FP at younger ages when methods are most likely to be successful (27, 28). Transvaginal ultrasound ovarian antral follicle count (AFC), antimüllerian hormone (AMH) testing or day 3 follicle–stimulating hormone (FSH) paired with estradiol levels can be used to assess ovarian reserve and predict response to controlled ovarian hyperstimulation. The results of ovarian reserve testing may help inform patient's decisions on if/when to pursue fertility preservation. These measurements should not be used to counsel patients about their fertility potential versus pregnancy (29).

There are data that suggest that *BRCA1* and *BRCA2* mutation carriers have diminished ovarian reserve, however this is controversial. Several cohort studies have shown earlier menopause among women with *BRCA1* and *BRCA2* mutations relative to controls, with premature menopause four times more likely in *BRCA* carriers than in controls (30, 31). Others demonstrated diminished ovarian reserve among mutation carriers as measured by response to stimulation, AMH levels and follicle count (32–35). However, other studies have not confirmed these findings (36, 37). Furthermore, studies have not shown that women with *BRCA* pathogenic variants have fewer pregnancies or more fertility problems (38–41).

Through ART, women have the option to cryopreserve and store oocytes, embryos or both. During an ART cycle, the ovaries are stimulated with exogenous gonadotropins followed by ultrasound-guided transvaginal needle aspiration of the oocytes. Once the oocytes are retrieved, they can be immediately cryopreserved or inseminated with sperm and then the resultant embryos may be cryopreserved. Oocytes and embryos may be stored effectively for many years. Of note, oocyte cryopreservation is no longer considered an experimental treatment (42).

Oocyte and embryo cryopreservation are effective strategies for FP, however, there are many important topics to discuss with patients who are considering these options. Patients should understand that by pursuing FP, live birth is not guaranteed; rather, oocyte and embryo cryopreservation are efforts to retain the opportunity to try to have a child using their own gametes. They should understand that success rates are highly dependent on age and may be influenced by other medical and lifestyle factors. In addition, success rates can vary by clinic. Women should also consider the optimal timing for FP, as well as the number of cycles they are willing to undergo to improve their chance of achieving a successful live birth. The risks of ART should be thoroughly reviewed. The use of fertility drugs is not associated with an increased risk for invasive breast, ovarian or uterine cancer in the general population of infertile women (43). However, many women who are at increased risk for these cancers have concerns about the effect of the high estradiol levels that are generated during ovarian stimulation on cancer risk. Fortunately, the use of fertility medications does not appear to increase the risk of breast cancer in breast cancer patients or *BRCA* mutation carriers (43). Nevertheless, efforts should be made to minimize the rise in estradiol levels by using an aromastase inhibitor (letrozole) plus gonadotropin stimulation protocol, which results in estradiol levels that are physiologic. In a study comparing a group of 120 breast cancer patients undergoing FP using gonadotropins with letrozole and 217 breast cancer patients who did not pursue FP, survival was not compromised. (44) In spite of limited data regarding safety of ART in women at high risk for gynecologic cancers, the data that do exist suggest that ART does not increase the risk of ovarian cancer in *BRCA* carriers, at least in the short term (45, 46).

4.2. Additional Options for Parenthood

4.2.1. Options for women after RRSO. If a woman has cryopreserved oocytes or embryos prior to RRSO, pregnancy can still be achieved by hormonally priming her uterus and performing an embryo transfer. However, if a woman does not have her own oocytes or embryos available to her, she may consider using donor oocytes, donor embryos or pursuing adoption.

4.2.2. Options for women who have had a hysterectomy. For a woman of reproductive age who has had a hysterectomy for endometrial cancer or for risk-reduction, but has retained her ovaries, having a child using her own gametes is still possible through IVF with a gestational carrier. Medical, legal, and psychological counseling is recommended for both the intended parents and the gestational carrier. The availability, legality and cost of gestational carrier IVF vary throughout the United States.

Uterine transplantation is a novel procedure that has recently resulted in live births, however, its role in preserving fertility in women with an increased risk for hereditary gynecologic cancers has not been determined (47).

5. GENETICS, TRANSMISSION AND REPRODUCTION

Individuals who carry an autosomal dominant pathogenic gene variant have a 50% risk of transmitting their gene mutation to offspring. As a result, some women who carry genes associated with hereditary cancer gene mutations face uncertainty about having children due to fear of having a child who will be at high risk for developing cancer. Unfortunately,

many women are not aware of medical technologies such as preimplantation genetic testing (testing an embryo prior to implantation) and prenatal diagnosis (testing a fetus during pregnancy) that can help minimize the risk of having a child who has the pathogenic variant.

5.1. Preimplantation Genetic Testing

Women who carry pathogenic gene variants that place them at high risk for cancer should be educated and counseled about preimplantation genetic testing (PGT) (48). For PGT, embryos are biopsied (typically at the blastocyst stage) and cryopreserved. The biopsies are analyzed in a genetics lab for monogenic/single gene defects (PGT-M), and based on the results, patients can preferentially select embryos for intrauterine transfer. Individuals who choose PGT-M also have the option of testing for aneuploidy (PGT-A). Many patients will elect to use both PGT-A and PGT-M because it allows identification of embryos that are both euploid and unaffected/non-pathogenic carriers. Thorough patient counseling by a reproductive endocrinologist and/or genetic counselor with detailed knowledge of the advantages and limitations of testing is essential.

For many people, PGT-M offers a desirable alternative to prenatal testing. Unlike prenatal testing, PGT-M allows identification of affected embryos prior to pregnancy, which may circumvent the stress associated with the knowledge of an affected pregnancy and prevent pregnancy termination. However, there are a number of important considerations that should be discussed when individuals contemplate its use. Women should be counseled that the number of embryos reaching the blastocyst stage is determined by multiple factors, such as age and ovarian reserve. Although it would be expected that approximately 50% of embryos would be affected by pathogenic gene variants patients should be aware of the possibility of having fewer embryos than expected (or even none) that are euploid and non-affected. In an observational study on the suitability of preimplantation genetic diagnosis for both *BRCA*-positive unaffected carriers and breast cancer survivors, 720 embryos were tested, identifying 294 (40.8%) as *BRCA*–negative (49). It is also important to discuss timing; women who cryopreserve oocytes should be informed that they can pursue PGT-M once they decide to fertilize their oocytes. Women who cryopreserve embryos but who are not yet ready to have a child may wish to defer testing until later, as identification of genes and genetic testing techniques continue to evolve. Finally, cost may influence whether women pursue this option or not. Unfortunately, fertility treatment (including IVF) is often not covered by insurance, and genetic testing may pose an additional cost to an already expensive treatment.

Interestingly, utilization of PGT-M is variable, even when individuals are aware of the technology. In a study of high-risk women, it was found that only 32.5% would theoretically use PGT-M themselves (50). Other studies have shown similar findings (51–53). However, it is imperative that patients are educated and counseled about its availability, as it may influence and promote informed reproductive decision-making.

5.2. Prenatal Diagnosis

Making decisions about PGT-M and prenatal diagnosis can be challenging. Prenatal diagnosis involves testing a fetus for the presence of a genetic mutation. For decades, physicians have used chorionic villus sampling (CVS) and amniocentesis to test for aneuploidy or structural chromosomal aberrations in a developing fetus at 10–14 weeks and 15–20 weeks respectively. Physicians now also use CVS and/or amniocentesis to generate a fetal karyotype as well as to detect the presence of a specific pathogenic variant. More recently, physicians have employed the technique of cell-free fetal DNA at approximately 10 weeks to evaluate for certain chromosomal abnormalities, but as of 2018 this test is still considered a screening test primarily for aneuploidy, and should not be used for prenatal diagnosis of a cancer risk gene (54). Based on the information from CVS or amniocentesis, parents may then decide whether or not to terminate a pregnancy. There may be moral and ethical considerations surrounding the decision to terminate a pregnancy for a pathogenic genetic variant which may or may not cause a future malignancy.

6. HORMONE REPLACEMENT THERAPY FOLLOWING RRSO

Approximately 60% of women with *a BRCA1* or *BRCA2* mutation undergo RRSO between the ages of 35–40 and thus enter menopause (55). Many women with Lynch Syndrome also elect THBSO to reduce uterine and ovarian cancer risk. There is a lack of guidelines specific to the follow up of women after RRSO. Proposed guidelines for follow up and health maintenance include yearly pelvic examination, discussion about CA-125 monitoring, encouragement for weight bearing exercise, calcium/vitamin D supplementation, dual-energy X-ray absorptiometry (DEXA) bone scan 1–2 years after RRSO, and consideration of HT in eligible patients (56). Surgical menopause in younger women can result in multiple symptoms that include severe vasomotor symptoms, vaginal dryness, sexual dysfunction, and cognitive changes, all of which may significantly affect quality of life (57). In addition, the risks of coronary heart disease and osteoporosis also increase (58).

The use of HT after oophorectomy in women at increased risk for gynecologic (and breast) cancers is controversial. Although HT is highly effective at reducing symptoms associated with menopause, the relationship between HT use and breast cancer risk even among women in the general population is complicated (59). Few studies have evaluated the safety of hormone therapy in women who have undergone risk-reducing surgery for *BRCA* mutations and there are no data on safety in women with Lynch Syndrome. A prospective study evaluating a cohort of women with *BRCA1* or *BRCA2* mutations after RRSO demonstrated that use of HT after oophorectomy in *BRCA1* carriers was not associated with an increased risk of breast cancer, although the cumulative incidence of breast cancer who used estrogen and progesterone was higher (22%) than in those who used estrogen alone (12%). Elective oophorectomy at the time of hysterectomy for the general population of women prior to age 50 has been associated with a significant risk of cardiovascular disease and an increase in all-cause mortality (60, 61). Given these risks as well as premature loss of estrogen

exposure in these patients, the benefits of HT may potentially outweigh the risks without an apparent increased risk of breast cancer (59). Therefore, it is reasonable to consider HT for women without a personal history of breast cancer. For women who are not candidates for HT or wish to avoid HT, non-hormonal options exist for treatment of vasomotor symptoms and include selective serotonin reuptake inhibitors (SSRIs), alpha 2 adrenergic agonists, dietary and lifestyle modifications, and alternative medicine approaches. Treatment of menopausal symptoms should be individualized and consider the potential risk versus benefit, medical history and therapeutic goals.

7. SUMMARY

- Women at risk for hereditary gynecologic cancers have unique concerns regarding cancer prevention, early detection, fertility and hormonal health.
- Surveillance, chemoprevention, and risk reducing surgical options are used to reduce gynecologic cancer risk but some may result in infertility and surgical premature menopause.
- There are multiple fertility preservation and family building strategies that can be used to help women achieve their procreative goals including oocyte and/or embryo cryopreservation, donor oocytes, donor embryos, gestational carriers, and adoption.
- Genetic testing can be used before embryo transfer or during pregnancy to identify whether embryos or fetuses carry a pathogenic gene variant, thereby reducing the risk of transmission.
- For women with surgical menopause who don't have a personal history of breast cancer, hormone therapy can be considered to avoid the negative consequences of hypoestrogenism.

8. CONCLUSION

Women at risk for hereditary gynecologic cancers can pro-actively reduce cancer risk through chemoprevention and risk-reducing surgery, but these interventions may affect future fertility and hormonal function. As access to genetic testing improves and the technologies of assisted reproductive technology advance, options available for management of at-risk individuals and couples will likely expand. Hormone therapy can improve symptoms of menopause and improve quality of life for women who experience premature surgical menopause. Collaboration between gynecologic oncologists and reproductive endocrinologists will further advance and improve the quality of care we provide to this unique patient population.

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Declaration of Competing Interest: Dr. Karen Glass reports I am on the executive of the Fertility Preservation Special Interest Group of the CFAS. I am on a team that created the CKN/CFAS National Oncofertility database in Canada. EMD Serono gave a grant to CKN to support the database build and launch. I didn't receive any of the funding and I don't have any other affiliation with CKN. I am the director of the Fertility Preservation Program at CReATe Fertility Centre. Lee-may Chen, Stephanie Blank, Elizabeth Burton, Emily Penick and Terri Woodard have no conflicts to declare.

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