Fertility counseling for patients with hereditary breast and ovarian cancer syndrome

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Purpose of the review
Among patients with hereditary breast and ovarian cancer, risk reduction strategies have a direct impact on fertility. In this review, we highlight the importance of early referral of those patients to fertility specialists for fertility planning, as the consideration for these risk-reducing procedures is overlaid with thoughts on childbearing.

Recent findings
Increased utilization of genetic testing has identified individuals with inherited pathogenic variants increasing risks of breast and ovarian cancer. For those patients, studies have identified potential areas for improvement including counseling on reproductive potential, fertility preservation, and the option for preimplantation genetic testing. Recent guidelines have emphasized the importance of consultation with a reproductive endocrinologist in the care of those patients.

Summary
Early referral to fertility specialists would ensure that reproductive concerns are met in a timely fashion and would facilitate future fertility planning, reviewing options for IVF, oocyte and embryo cryopreservation, and consideration of preimplantation genetic testing.

Keywords
BRCA, fertility preservation, hereditary cancer, preimplantation genetic testing

BACKGROUND

Inherited pathogenic variants increasing risks of ovarian and breast cancer can lead to interventions for risk reduction or treatment of cancer that are associated with a direct impact on future fertility.

The elevated risk of developing breast and ovarian cancer is mostly seen with germline mutations in *BRCA1* or *BRCA2* genes [1]. Pathogenic variants in other genes such as *ATM*, *BRIP1*, *MLH1*, *PALB2*, *RAD51C*, or *RAD51D* can also be associated with an increased risk of developing breast or ovarian cancer. As *BRCA1* and *BRCA2* pathogenic variants are highly penetrant, and account for most hereditary breast and ovarian cancer cases, they would be the focus of this review.

BRCA1 and *BRCA2* are tumor suppressor genes involved in the repair of double-strand DNA breaks, specifically through the homologous recombination pathway [2].

BRCA1 and *BRCA2* account for almost 85% of hereditary breast and epithelial ovarian cancer cases [3], and like other hereditary cancer syndromes, these cancers often occur at an early onset of age than is observed in the general population.

Breast cancer often occurs during the reproductive years [4]. Patients with *BRCA1* mutation have a lifetime risk of developing breast cancer of 65% and an ovarian cancer risk of 39%, while the risk of breast cancer is 45% and the risk of ovarian cancer is 17% in *BRCA2* mutation carriers [5].

Pancreatic cancer risk is increased in both *BRCA1* and *BRCA2* mutation carriers [6]. Male *BRCA1* and *BRCA2* mutation carriers also face a higher lifetime risk of breast cancer, and with *BRCA2* mutation, they are also at risk for prostate cancer [6]. The prevalence of *BRCA* deleterious mutations is one in 300 to one in 465 in the general population [7], but there are some populations in which the prevalence is higher, such as those of Ashkenazi Jewish ancestry (one in 40) [8].

BRCA1 and *BRCA2* mutations are inherited in an autosomal dominant pattern, with incomplete penetrance [3]. People who are carriers of an

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KEY POINTS

- Inherited pathogenic variants increasing risks of breast and/or ovarian cancer can lead to risk reduction intervention or cancer treatments that would have a direct impact on future fertility.
- Early referral to fertility specialists is important for the discussion of future fertility, reviewing options for IVF, oocyte and embryo cryopreservation, and consideration of preimplantation genetic testing.
- Fertility planning can be informative for patients to aid them in considering options for risk-reducing procedures, as future pregnancy may be achieved with the uterus in place if eggs/embryos are cryopreserved, with or without fallopian tubes or ovaries.

autosomal dominant pathogenic gene variant have a 50% risk of passing their genetic mutations to their biological offspring.

RISK REDUCTION

Oral contraceptive pills (OCPs) were shown to have a duration-dependent reduction by 50% in ovarian cancer risk in the general population when used for 10 years or longer [9]. OCPs can also decrease the risk of ovarian cancer in *BRCA 1/2* carriers [10]. While OCPs can have protective benefits against ovarian cancer, the risk of OCPs use on breast cancer development in those patients has been inconsistent among studies, but recent data suggest that *BRCA* mutation carriers should be counseled on increase in the risk of breast cancer with the use of OCPs, especially in *BRCA1* mutation carriers when used for longer durations [11]. Levonorgestrel intrauterine device has been shown to reduce the risk for ovarian cancer in the average-risk population [12].

Risk-reducing salpingo-oophorectomy (RRSO) is the most effective method in reducing the risk of ovarian cancer with a reduction of up to 70–85% [13]. RRSO has shown to be associated with a reduction in breast cancer mortality, all-cause mortality in high-risk groups, and it is recommended as soon as childbearing is completed, between the age of 35 and 40 years in *BRCA1* mutation carriers and between the age of 40 and 45 years in *BRCA2* mutation carriers [14▪▪].

With RRSO, in addition to the direct impact on natural fertility, the loss of ovarian hormone production would result in premature menopause for patients undergoing the procedure before the average age at menopause of 51 years. Early surgical menopause in the general population is associated with adverse health effects including osteoporosis, cardiovascular disease, and all-cause mortality [15]. Hormone therapy is recommended for those patients to reduce those risks and for the management of menopausal symptoms [16], but safety data in *BRCA 1/2* mutation carriers are limited [17].

Because the majority of high-grade serous ovarian cancers originate in the fallopian tube, bilateral complete surgical removal of fallopian tubes (bilateral salpingectomy) may decrease the risk of serous ovarian cancer; however, there are no prospective data showing the actual risk reduction in a high-risk population and RRSO is still the recommended standard of care in this population [18▪]. Unlike RRSO, bilateral salpingectomy alone does not reduce the risk of breast cancer. As a result, bilateral salpingectomy should be reserved to women who decline RRSO at the recommended age, and they should still be encouraged to eventually undergo bilateral oophorectomy.

While the overall risk of endometrial cancer is not increased for patients with *BRCA* mutations, limited data suggest that there may be a slightly increased risk of serous uterine cancer among *BRCA1/2* mutation carriers [19], so there should be a discussion on the risks and benefits of concurrent hysterectomy at the time of RRSO [14▪▪]. Hormone therapy for patients who had a hysterectomy with their RRSO surgery would be with estrogen only without the need to add progestin [18▪]. Estrogen only therapy may be associated with lower risks.

Risk reduction procedures and cancer treatment's impact on reproduction is summarized in Table 1.

Table 1. Impact of interventions for patients with *BRCA 1/2* pathogenic mutation

Intervention	Possible impact
Risk-reducing salpingo-oophorectomy	Loss of natural fertility and ovarian hormone production: premature menopause
Risk-reducing salpingectomy	Loss of natural fertility. Fertility is possible with the use of assisted reproductive technologies
Treatment of breast cancer	Chemotherapy can have a direct impact on the ovaries that may lead to loss of natural fertility and ovarian hormone production: premature menopause
Treatment of ovarian cancer	Loss of natural fertility and ovarian hormone production: premature menopause

REFERRAL TO FERTILITY SPECIALIST

Women who are found to be carriers for pathogenic *BRCA 1/2* mutations face two 'biological clocks'. The first is related to the natural age-related fertility decline, which would result in lower chances of pregnancy and higher risks of miscarriage primarily because of aneuploidy within the embryos. Other age-related factors include accrued impact of gynecologic disease, medical comorbidities, and infection, among others [20,21].

The second biological clock is about completing childbearing before undergoing the recommended risk-reducing surgery by age 35–40.

These future fertility plans can be impacted by many factors. Among which is whether these patients are partnered or not, the desired number of future pregnancies, and the ideal timing of those pregnancies.

Early referral to a fertility specialist for discussion on future reproductive options is recommended if it is not feasible to complete childbearing before the recommended age for risk-reducing surgery, as the consideration for these procedures is overlaid with thoughts on childbearing [22].

Having these discussions with a fertility specialist early on is important since most non-fertility providers are not well-versed in the available fertility options which would limit their ability to participate in fulsome discussions. For a shared decision-making, the physicians must have the medical expertise to guide patients through their decision, but they must also understand patients' values to appropriately frame the decision according to what the patient needs [23]

Prior research has indicated that *BRCA* mutation carriers would prioritize having biological children over the recommended prophylactic surgery, suggesting that family goals may act, even temporarily, as barriers to prevention for women who wish to have children [24].

There are many considerations for undergoing the recommended risk-reducing surgeries in addition to loss of future fertility, these include surgical menopause and change in sexuality and body image [23].

The discussion would review the patient's family goals, timing, and whether they are actively engaged in conception plans at that time. The decision to proceed with these risk-reducing procedures is not an easy one for many reasons, including the involvement of their partner in decision-making, the uncertainty surrounding their cancer status, a shortened reproductive timeline, and the consideration of gene inheritance [25]. Prior research indicated that those patients expressed the need for decision-making support [26]. Ultimately, family planning is a deeply personal choice [23].

Ovarian reserve assessment can be evaluated at the time of the visit, for baseline evaluation. Some studies have suggested that patients carrying *BRCA* mutations have lower ovarian reserve, measured by anti-mullerian hormone level, antral follicle count, and response to stimulation [27,28]; however this is controversial as other studies have not confirmed these findings [29,30]

Following these initial assessments, the discussion would revolve around fertility planning.

This early referral allows women who are interested to pursue fertility preservation at younger ages when the likelihood of future pregnancy is higher.

Fertility preservation with oocyte or embryo cryopreservation would offer significant advantages. These options would increase chances of conception in the future, and specific to those patients, may be associated with a shorter time to pregnancy depending on age at presentation, and the possibility to undergo the recommended salpingo-oophorectomy or bilateral salpingectomy, while maintaining the ability to transfer embryo(s) in the future when ready for conception.

Assisted reproductive technologies for freezing eggs or embryos would involve ovarian stimulation with gonadotropins, retrieving the eggs, and either freezing mature oocytes to be fertilized in the future or fertilizing them and freezing embryos (IVF).

A major advantage of IVF in this population is the option of preimplantation genetic testing on the embryos. Embryo trophectoderm (the portion of the embryo that would form the placenta) biopsy and testing are commonly performed during IVF treatment cycles for aneuploidy testing to aid in selecting a chromosomally balanced embryo for future embryo transfer, thereby increasing chances of pregnancy per embryo transfer. In this patient population, embryo biopsy can be also used to test for the *BRCA* mutation and potentially select unaffected embryos to transfer in the future (see below).

Embryos can be transferred to the uterus even after RRSO, as hormones can be used to support early pregnancy. Cryopreservation of oocytes or embryos can also be important for those patients that end up with hysterectomy with their risk-reducing surgery, as embryos can be transferred to a gestational carrier in the future if desired.

Gonadotropins used to stimulate multifollicular development in the ovaries would be associated with a significant rise in estrogen levels. Current data indicate that these fertility treatments and the related rise in hormone levels are not associated with increased risks of cancer [31].

This has also been seen in patients with breast cancer who underwent fertility treatments without increased risk of relapse or breast cancer-specific mortality [32]

Limited research has also shown that fertility treatments do not adversely impact breast cancer risk in *BRCA* carriers [33]. Further larger studies are required to confirm these findings in *BRCA* mutation carriers given their inherent increased susceptibility to cancer [34].

The cost of fertility preservation treatments is one of the limitations to many patients. These procedures are not typically covered by health insurance plans.

PREIMPLANTATION GENETIC TESTING

Given the 50% risk of transmitting *BRCA* mutation to offspring, the decision of having children may be impacted by the fear of having a child affected by the mutation and at high risk of developing cancer. This uncertainty can be mitigated by knowledge of medical technologies to facilitate genetic testing for the pathogenic mutation through the process of preimplantation genetic testing for monogenic disorders (PGT-M). This is different than prenatal testing that is performed during pregnancy by chorionic villus sampling or amniocentesis. The major advantage of PGT-M to prenatal testing is deciding on embryo selection and transfer prior to pregnancy rather than deciding on terminating the pregnancy of an affected fetus.

The decision to perform genetic testing on embryos can be controversial and a topic of debate because of the late onset, incomplete penetrance, and availability of preventive and therapeutic options [35].

Personal experiences of suffering and loss because of cancer can profoundly affect perceptions of the risk and severity of *BRCA* mutations and perhaps interest in PGT-M [36], and they may be more likely to undergo prophylactic risk-reducing surgeries [37].

The testing of their embryos would reduce the uncertainty and can give the sense of increased control over their inherited risks.

Prior studies on *BRCA* mutation carriers have reported their feeling of guilt about transmitting the mutation to future children [38] and up to 90% in one study were concerned about passing the mutation to their offspring [39].

Needless to say, the decision to test the embryos for *BRCA* mutation is complex and depends on a variety of personal and ethical issues. Opinion surveys have shown that the majority of *BRCA* mutation carriers are supportive of offering PGT-M to others as an acceptable reproduction option [40].

In a focus group conducted among unaffected carriers, the majority of women held positive attitudes toward preimplantation genetic testing to reduce transmission to future offspring [22].

The number of embryos that are unaffected by the mutation depends mostly on patient's age at presentation, and their ovarian reserve. Often, testing embryos for aneuploidy is done at the same time. Given the likelihood of fewer embryos that are eligible for transfer, patients may decide on undergoing more than one IVF treatment cycle.

Patients need to prepare for possible scenarios when there are no euploid embryos unaffected by the mutation. They would need to decide whether they would accept the transfer of an embryo affected by the mutation, or whether they would choose to transfer a male embryo with the mutation given a different risk profile.

Studies have identified a knowledge gap in this subject and further identified unmet needs for education and support for decision-making [22]. *BRCA* mutation carriers have indicated that fertility options and preimplantation genetic testing were not well-discussed by their healthcare providers. Barriers to fertility discussion among cancer patients have included a lack of knowledge, training, and fertility preservation guidelines among physicians [22,41].

It is anticipated that the interest in PGT-M for *BRCA* mutation testing is likely to grow because of increased availability and awareness of *BRCA* testing among younger, unaffected individuals and the expanded use of assisted reproductive technologies [36].

Other parenthood options such as adoption and using donor gametes can be discussed with those patients during their consultation with the fertility specialist.

CONCLUSION

Early referral of patients with hereditary breast and ovarian cancer to reproductive specialists can ensure that fertility concerns are met in a timely fashion and can facilitate planning fertility preservation, preventive strategies, and if desired, preimplantation genetic testing.

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Conflicts of interest

None.

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- ■ of special interest
- ■■ of outstanding interest

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