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EDITORIAL

Fertility in Women with *BRCA1* and *2* Mutations — Do We Need to be Concerned?

The *BReast CAncer susceptibility gene 1* and *Breast Cancer susceptibility gene 2* (*BRCA-1* and *2*) are "tumor suppressor genes" that play an essential role in maintaining the DNA integrity.[1] Mutations in these DNA double-strand breaks (DSBs) repair genes predispose an individual to various malignancies. While both the *BRCA1* and *2* mutations confer an increased risk of breast, ovarian and pancreatic cancer, mutation in the *BRCA1* gene increases the probability of developing cancers of the colon, uterus and uterine cervix and *BRCA2* can increase the chances of melanomas, stomach, gallbladder and bile duct cancers. The estimated lifetime risk in female carriers of these mutations is 65–80% for breast cancer and 20–45% for ovarian cancer.[2] In addition, the cancers in mutation carriers occur almost a decade earlier compared with those without the mutations.

Hence, many young women with *BRCA* mutations, either due to cancer prevention strategies or cancer-related treatments can have a deleterious impact on their fertility and opportunity to become genetic parents. Thus, potential barriers and concerns about fertility preservation need to be addressed in these women prior to any related intervention.

In those diagnosed with cancer, the alteration in ovarian reserve may occur due to the gonadotoxic treatment superimposed with the natural aging that may result during the course of treatment. The DNA abnormalities along with the damage to somatic and germ cells caused by various chemotherapeutic drugs can lead to the arrest of the normal proliferation in the cell cycle including apoptosis, vascular injury and follicular burnout resulting in an estimated loss of up to 10 years of ovarian reserve. The risk of chemotherapy-induced amenorrhea seems to be higher for *BRCA2*-mutated patients as compared with those with *BRCA1* mutations. In women with hormone receptor-positive breast cancer, extended hormone treatment of 5–10 years can further delay the pregnancy, thus narrowing the already compromised reproductive period. Hence, markers of the follicular ovarian status need to be systematically measured before administration of anticancer treatment.

Besides the effect of anticancer therapies, *BRCA* mutations by itself can have a negative impact on ovarian function inherent to its genetic status. Although early onset of menopause has been reported in both *BRCA1* and 2-mutated patients, a study by Rzepka-G´orska et al., observed a premature menopause by almost 3 years in *BRCA1*-mutated carriers as compared with those with *BRCA2* mutations.[3] There are conflicting reports regarding difference in anti-Müllerian hormone (AMH) in those with *BRCA1/2* mutations. Whereas, Jhonson, et al. have reported lower levels of AMH in *BRCA2*-mutated patients,[4] Wang et al. reported lower AMH levels in those with *BRCA1* mutation in women more than 35 years of age.[5] In addition to the inherent factors with *BRCA* mutations, the recommendation of risk-reducing salpingo-oopherectomy by the American College of Obstetricians and Gynecologists after completion of childbearing or nearing 40 years of age, further pushes these women to take timely fertility decisions.

So, given the narrow reproductive period, should we counsel *BRCA* carriers to have early pregnancies? With increasing age at first pregnancy, struggling careers, urbanization, and lack of adequate information regarding the predispositions and pregnancy outcomes in BRCA mutation carriers, this indeed seems to be a challenging task for both physicians and mutation carriers. There is a relative paucity of data regarding the pregnancy outcomes, however, the limited evidence does not suggest a difference in parity age at first pregnancy increases in infertility compared with the noncarriers. Nevertheless, the assumption that *BRCA* mutations may have an adverse impact on fertility is based on the hypothesis that since telomere length correlates with reproductive lifespan, hence deficiencies in the repair of DSB and telomerase shortening associated with *BRCA* mutations may predispose to apoptosis. These have been confirmed in vitro studies where *BRCA* mutations may be associated with premature follicular depletion and apoptosis.

Of the assisted reproductive techniques, response to ovarian stimulation in *BRCA*-mutated patients is conflicting with a recent study reporting comparable oocyte yield, number of zygotes produced and fertilization rates between *BRCA* mutation carriers and non-carriers. Contrarily, there is also evidence to suggest that *BRCA1* mutations are associated with a poor response to ovarian stimulation with up to a nearly 25% increase in risk to a poor response.

Oocyte and/or embryo cryopreservation is the most accepted and reliable fertility preservation method (after pubertal onset). In order to limit estradiol rise induced by ovarian stimulation, specifically in estrogen-sensitive diseases, such as breast or endometrial cancer, specific co-treatment with aromatase inhibitor (letrozole) is currently proposed. The evidence for effectiveness of oocyte preservation in patients with breast cancer is meagre and even scantier for *BRCA*-mutated women. As far as safety is concerned, there is no reported increased risk of gynecologic or breast cancers, even in healthy *BRCA* mutation carriers.

Ovarian tissue cryopreservation seems to be only strategy allowing for preservation of both fertility and endocrine ovarian function. Considering the general recommendation of bilateral salpingo-oophorectomy between 40 and 45 years, or before the age of the earliest case of ovarian cancer in the family, the role of ovarian tissue cryopreservation is uncertain. However, if one might consider this option, very young patients would be the best candidates, in particular, if embryo/oocyte cryopreservation following controlled ovarian hyperstimulation cannot be performed. In *BRCA*-mutated women, the success of ovarian tissue cryopreservation, given the probability of poor ovarian reserve and possibility of malignant transformation of the preserved ovarian tissue, is debatable. Also, the fear of transmitting the mutation to the offsprings may deter the women from preserving their fertility. In such situations, preimplantation genetic diagnosis (PGD), which allows selective transfer of normal embryos, provides an opportunity of elimination the transmission of these mutations to their progeny.

Preimplantation genetic diagnosis is now considered acceptable for conditions like hereditary breast and ovarian cancer according to the European Society of Human Reproduction and Embryology ethics taskforce.[6] The procedure involves ovarian stimulation and oocyte harvesting and availability of the sperm for in vitro fertilization. The embryos are fertilized and developed in the embryology

laboratory. At fifth and/or sixth of development, the external cells of the blastocyst can be biopsied and tested for the presence of *BRCA1* or *2* mutations.

Besides the potential benefit of PGD in *BRCA* carrier/mutated women, there are many associated ethical issues. Since not all *BRCA* carriers develop cancers and the related cancers may be curable with availability of effectual treatment, ensuring ethical practice of PGD could be a matter of concern. Nevertheless, despite these arguments, the distress and apprehensions involved in these women, ethically justify the use of PGD. So far, approximately 150 cases of PDG have been performed worldwide for *BRCA1/2* mutations. In India, the first PGD for *BRCA1* mutation was carried out in the year 2018.

To summarize, fertility preservation discussions and preservation of the potential to have biological offsprings are important for both survivors and previvors with *BRCA* mutations. However, a number of obstacles and concerns exist regarding preservation of fertility and future pregnancy in *BRCA* carriers including benefit, success, scheduling, and safety of any intervention. A multidisciplinary team approach involving oncologists, reproductive endocrinologists and psychosocial support providers is required to help women in making the best decisions for themselves keeping in view their medical and social situations.

References

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