

## Caring for BRCA Carriers: Strategies to Promote Health and Preserve Fertility

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Received Date: February 05, 2018; Accepted Date: March 02, 2018; Published Date: March 08, 2018

Citation: Nola S. Herlihy (2018) Caring for BRCA Carriers: Strategies to Promote Health and Preserve Fertility. J Womens Health Gyn 5: 1-10.

### Abstract

BRCA1 and BRCA2 mutation carriers are at increased risk for breast and ovarian cancer, with lifetime risks approximately 49-72% for breast cancer and 17-59% for ovarian cancer. The National Cancer Comprehensive Network recommends routine screening as well as a risk-reducing surgery to remove the fallopian tubes and ovaries for BRCA carriers between ages 35 to 40 or after the completion of childbearing. Since many women have not completed childbearing by age 40, they have the option of undergoing fertility preservation prior to undergoing this risk-reducing surgery. Additionally, use of Preimplantation Genetic Diagnosis (PGD) allows couples to prevent transmission to their offspring. BRCA carriers may be at greater risk for diminished ovarian reserve, yet studies regarding the effect of BRCA carrier status on fertility remain inconsistent in their conclusions. To date, researchers have demonstrated that infertility treatment is safe in BRCA carriers. BRCA carriers are faced with complex challenges and will benefit from consultation with a fertility specialist to discuss options for fertility preservation to safely build the family they desire.

**Keywords:** Breast neoplasms; Ovarian neoplasms; Fertility; Cryopreservation; Preimplantation genetic diagnosis

### Introduction

The majority of breast and ovarian cancers result from sporadic mutations. Of women with breast cancer, approximately 15% will have at least one affected relative, demonstrating that a minority are due to hereditary cancer syndromes [1]. BRCA1 and BRCA2 germline mutations are understood to influence up to 20% of hereditary breast and ovarian cancers, 10% of ovarian and 3-5% of breast cancer [2,4]. BRCA is estimated to be 0.33-0.13% of the general population [5] with the highest prevalence in the Ashkenazi Jewish community (3%) [6]. The BRCA genes are tumor suppressor genes, which encode proteins responsible for DNA mismatch repair. BRCA carriers are susceptible to an accumulation of damaged DNA that could contribute to increased cancer risk and earlier onset of cancer development [6]. BRCA carriers have a lifetime-estimated risk of breast (49-72%) and ovarian (17-59%) cancer (table 1) [7-9].

Vigilant screening recommendations are standard. Often, risk-reducing surgery (i.e. removal of the fallopian tubes and ovaries) is performed after the conclusion of family building in affected women between age 35-40 [10]. Given that many patients have not yet completed child bearing by this age, fertility preservation through cryopreservation of oocytes and/or embryos should be considered prior to surgery. Clinicians must convey realistic expectations regarding patient prognosis, as BRCA carriers may be at risk for diminished ovarian reserve (DOR). This clinical perspective summarizes breast and ovarian cancer preventative strategies, tours fertility preservation and family building options, discusses potential BRCA and DOR association, and explores ovarian stimulation in BRCA carriers.

	Lifetime Breast Cancer Risk	Lifetime Ovarian Cancer Risk
BRCA 1	57-72%	40-59%
BRCA 2	49-69%	17-18%
General Population	12%	1.4%

Table I. Risk of cancer in BRCA patients [7-9].

### Cancer Prevention: Screening Strategies and use of Prophylactic Surgery

Current guidelines for breast cancer screening in BRCA carriers recommend clinical breast exams every 6 months and annual MRI or mammogram beginning at age 25 - or sooner - depending on the earliest age of onset in the family [11]. A combination of clinical breast exam, mammography and MRI has the highest sensitivity for detecting breast cancer [12-13].

Prophylactic surgery and chemoprevention are two ways to reduce the risk of breast cancer development. According to the National Comprehensive Cancer Network (NCCN) guidelines, women with BRCA mutations may be offered prophylactic mastectomy. Prophylactic bilateral total mastectomy has shown to reduce the rate of breast cancer by 92% and related deaths by 81% in healthy BRCA carriers [14,15]. A large prospective multi-center cohort study of 2,482 women with a known BRCA mutation demonstrated that 100% of women who underwent risk-reducing mastectomy did not develop breast cancer while 7% of those who did not have surgery developed cancer within the 35 year span of the study [16]. Although its efficacy and safety requires further research, Tamoxifen, a selective estrogen-receptor modulator (SERM), has shown to be a promising chemoprevention agent to prevent and/or treat breast cancer.

Prevention strategies for ovarian cancer are similar to those for breast cancer, including early surveillance and prophylactic surgery. NCCN guidelines advise clinicians to consider concurrent transvaginal ultrasound and CA-125 every six months beginning at age 30, or 5 to 10 years before the earliest onset of a family diagnosis of ovarian cancer [11]. However, screening appears to have limited benefit as it has not been shown to decrease mortality, especially with high-risk patients. Chemoprevention with the use of oral contraceptive pills (OCPs) is a plausible consideration, as OCPs have been shown to decrease the risk of ovarian cancer in BRCA carriers and the general population. However, the risk of ovarian cancer remains high, and BRCA carriers may forego the use of OCPs due to the potential increased risk of breast cancer [17]. Due to limited options for prevention, risk-reducing bilateral salpingo-oophorectomy (BSO) is advised at age 35-40 or after childbearing completion. A BSO reduces the risk of ovarian and primary peritoneal cancer by 80% in BRCA carriers [18]. Mounting evidence demonstrates that ovarian cancer originates in the fallopian tubes, hence, interval salpingectomy with delayed oophorectomy (ISDO) has been suggested for women wishing to delay oophorectomy [19].

Kwon et al performed a cost-benefit analysis of BSO, bilateral salpingectomy and ISDO, and found that BSO was associated with lowest cost and highest life expectancy, but ISDO yielded the highest quality-adjusted life expectancy [20]. However, the use of ISDO increases the potential for surgical complications as it requires two, separate surgical procedures. Given that the protective benefit of ISDO is still uncertain and the need for two procedures may lead to decreased compliance, the technique is not the standard of care and should only be considered for women who decline oophorectomy. Surgically-induced premature menopause carries its own health consequences including vasomotor symptoms and decreased sexual function as well as increased risk for cardiovascular disease and osteoporosis. BRCA carriers without a history of breast cancer should consider hormone replacement therapy (HRT) after surgery to mitigate these effects; HRT has not been associated with increased risk of breast cancer in this population [21].

### BRCA and Infertility

The pathophysiologic mechanisms connecting BRCA mutations and infertility are not well understood, however a variety of links have been proposed. BRCA mutations may affect ovarian function by decreasing ovarian reserve, defined as oocyte quantity, quality, and reproductive potential [22]. BRCA1 and BRCA2 are part of the family of ataxia-telangiectasia-mutated (ATM)-mediated DNA double strand repair genes, and have critical roles in the DNA repair pathway. Inefficient repair causes DNA damage accumulation and contributes to oocyte aging, apoptosis, and depletion [23,24]. Titus et al. published findings in which BRCA1 heterozygous mutant mice produced fewer oocytes in response to ovarian stimulation and had smaller litter sizes than wild-type cohorts. Furthermore, the total primordial follicle numbers per mouse ovary were lower and a significantly higher percentage of follicles accumulated DNA damage as a result of deficient double stranded break repair [25].

BRCA mutations have been postulated to influence oocyte rates of aneuploidy. Primarily oocytes utilize DNA repair mechanisms while undergoing homologous recombination prior to meiotic arrest. Failure to repair the double stranded DNA correctly leads to deletions, translocations, and chromosome loss [26,27]. A mouse model study demonstrated that BRCA1 is required for meiotic spindle assembly and checkpoint activation, for which any disruption could lead to aneuploidy [28]. There is limited data on the risk of embryo aneuploidy in BRCA carriers; however, one IVF study demonstrated no significant difference in the rate of aneuploidy in BRCA 1 and 2 carriers [29]. BRCA1 is further known to play a role in maintaining genome integrity and mutations are associated with reduced cell proliferation and impaired embryogenesis [23,30,31]. To date, there are no published studies comparing the incidence of embryonic aneuploidy among BRCA carriers and non-BRCA control patients undergoing IVF.

### Diminished Ovarian Reserve in BRCA Carriers

The literature remains inconclusive regarding the potential links between BRCA gene mutations and decreased ovarian reserve, but many studies suggest a direct relationship. Reduced parity, often observed in BRCA carriers, may reflect DOR in these patients [32]. However, parity is not a reliable marker of ovarian reserve as it could be influenced by patient preferences for family size, apprehension for BRCA heredity, and use of risk-reducing BSO. Additionally, two studies have demonstrated early onset of natural menopause in BRCA mutation carriers. A cohort comparing 382 BRCA carriers to 765 non-carriers showed a significantly younger mean age of menopause (50 vs 53 years,  $p < 0.001$ ) [33]. Finch et al. similarly displayed a decrease of 2 years in menopause for BRCA1 carriers and a decrease of a year in BRCA2 carriers in a case control of 908 matched pairs [34]. Several studies examining the association between anti-Müllerian hormone (AMH) levels, a well-known marker of ovarian reserve, and BRCA carrier status show conflicting data. A small study of 41 healthy BRCA carriers failed to demonstrate a statistically significant difference in AMH levels compared to the general population [35]. Two studies have suggested that the BRCA1 mutation maybe implicated in DOR to a greater degree than the BRCA2 mutation. A study of 143 healthy reproductive-age women stratified BRCA1 and BRCA2 carriers and found, after controlling for age and BMI, that BRCA1 carriers have a significant decrease in serum AMH levels as compared to non-carriers (0.53ng/mL [95% confidence interval (CI) 0.33-0.77 ng/mL] vs. 1.05 [95% CI 0.76-1.40 ng/mL]). BRCA2 carriers showed no difference in AMH levels as compared to non-carriers [36]. Philips et al. corroborated these findings in a cross sectional study of 693 women with BRCA1 or BRCA2 without a personal history of cancer. On average, BRCA1 carriers had 25% (95% CI: 5%–41%,  $P < 0.02$ ) lower AMH concentrations than non-carriers; and BRCA2 status, once again, was shown to have no effect on AMH level [37]. However, when comparing BRCA carriers and women at high risk for hereditary breast and ovarian cancer who are BRCA negative to low risk women, Johnson et al found that BRCA2 carriers and BRCA negative women have lower AMH levels than low risk women [38].

Three studies focused on DOR and ovarian response to IVF in BRCA carriers. In a study of 12 young breast cancer patients undergoing controlled ovarian hyperstimulation with co-administration of gonadotropins and letrozole, BRCA1 carriers demonstrated significantly reduced oocyte yield compared to controls and a third of carriers had low ovarian response [39]. Low ovarian response is largely accepted as less than four oocytes at vaginal oocyte retrieval (VOR) [39]. Notably there was no significant difference in ovarian response or oocyte yield between BRCA2 carriers and non-carriers. Derks-Smeets et al confirmed these findings in a retrospective study of 38 BRCA carriers and 154 controls, with multiple linear regression analysis revealing significantly lower yield of mature oocytes in BRCA1 patients [40]. However, a larger case-controlled study of 62 BRCA mutation carriers and 62 matched controls reported similar oocyte yields at VOR (13.75 vs. 14.75) and similar rates of low ovarian response among the patient cohorts (8.06% vs. 6.45%) [41].

More recently, Lin et al made a compelling argument for diminished ovarian reserve in BRCA carriers by demonstrating lower primordial follicle densities and higher DNA double-stranded breaks in primordial follicle oocytes in ovarian tissue samples from BRCA carriers compared to age matched controls [42].

### Options for Fertility Preservation

Healthy BRCA mutation carriers are faced with several factors that may influence their decisions to conceive and include:

- If, and when, to undergo risk-reducing surgery, particularly the removal of the fallopian tubes and ovaries
- The potential risk of diminished ovarian reserve
- Age, which plays a role in all women's fertility
- Marital status
- Desired family size
- The risk for passing on the mutation to their offspring (as high as a 50% chance)

Although adoption and the use of gametes from unaffected donors in third party reproduction are available avenues to parenthood, most BRCA carriers prefer biological offspring [43,44]. Therefore, counseling patients on their reproductive options and potential impact on well-being is crucial.

BRCA carriers have options for family building. They may try to conceive naturally and elect for genetic testing of their offspring, such as prenatal diagnosis (PND), to prevent the transmission of the BRCA mutation. Alternatively, women have the option to utilize controlled ovarian hyperstimulation (COH) followed by oocyte or embryo cryopreservation and preimplantation genetic diagnosis (PGD). With cryopreservation techniques, BRCA carriers who desire to extend their fertility can preserve it prior to undergoing risk-reducing surgery.

Given the modern improvements in cryopreservation technique, thousands of women have conceived using vitrified, thawed, fertilized, and transferred oocytes. As demonstrated by studies finding no increase in chromosomal abnormalities, birth defects, or developmental deficits in the offspring, oocyte cryo preservation is considered a safe laboratory technique [45-47]. The improved efficacy of oocyte cryopreservation is further evidenced by the release of the American Society for Reproductive Medicine (ASRM) committee opinion in 2013, which states oocyte vitrification and warming "should no longer be considered experimental" [48].

Alternatively, retrieved oocytes can be fertilized and frozen as embryos. One of the advantages of freezing embryos is that they can be biopsied prior to freezing, which allows for PGD to test for the BRCA mutation and preimplantation genetic screening (PGS) to test for embryonic aneuploidy. With PGD, trophectoderm cells from embryos cultured during in vitro fertilization (IVF) are biopsied, and a genetic analysis screens embryos for the BRCA mutation. By selecting unaffected, healthy embryos, clinicians may assist patients in preventing transmission of the BRCA mutation to their offspring [49-51].

Focus group data demonstrated that BRCA carriers are interested in fertility preservation but feel health care providers do a suboptimal job of discussing these options and concerns [52]. Some of these patients require greater familiarity in the reproductive clinical impact of a risk-reducing BSO on subsequent fertility or the benefit of fertility preservation consultation (i.e. oocyte or embryo banking) before undergoing a risk-reducing BSO [53]. Furthermore, most of these women have voiced tremendous emotional distress and worry about passing on the mutation to their offspring [54-57]. Most couples consider termination of an affected fetus as unacceptable, and favor PGD over PND as a means of BRCA prevention [58]. The use of PGD for the detection of BRCA mutations raises potential ethical concerns and highlights the issue of parental autonomy in reproductive decision-making [59-61]. Attitudes towards PGD are mixed, but most women surveyed believe PGD should be offered as part of clinical care and the ethical concerns are outweighed by the potential benefit of rearing healthy offspring(s) [43]. A study of couples with a known BRCA mutation who used PGD cited protection of their future children from the physical and psychological effects of BRCA as their primary motivation [58]. Furthermore, decisions are dictated by patients' own experiences with disease; those with a personal history of cancer and greater severity of disease are more likely to consider using PGD [62]. Similarly, nearly half of surveyed gynecologists and gynecologic oncologists in the United States believe PGD to be "appropriate" in the detection of cancer predisposition due to BRCA [63]. Despite these findings, data continues to highlight a lack of knowledge in BRCA carriers on fertility preservation options [53,64]. Therefore, all patients determined to be a BRCA carrier would seem to benefit from a consultation with a reproductive specialist prior to undergoing medical or surgical management [65-67].

Fertility specialists can apply treatment algorithms for BRCA mutation carriers who have not yet completed child-bearing based on their age, relationship status and whether they plan to utilize PGD (Figure 1 and 2). BRCA carriers have the option to undergo oocyte cryopreservation at any age, and should strongly be encouraged to consider this option if they are over the age of 35. Younger women under the age of 35, who are not yet ready to commit to having oocytes cryopreserved, may elect for annual monitoring of ovarian reserve (serum AMH level and transvaginal sonogram to assess a follicle count), with the goal of pursuing oocyte cryopreservation before any significant decline in ovarian reserve. Those with cryopreserved oocytes have the option of also undergoing PGD in the future.

BRCA carriers who plan to utilize PGD in the future to prevent transmission of BRCA to their offspring should be counseled by an IVF specialist as early as possible to maximize the number of embryos available for genetic screening and banking. Women undergoing PGD tend to also undergo aneuploidy screening simultaneously (PGS, preimplantation genetic screening, or CCS, comprehensive chromosomal screening). Aneuploidy is the leading cause of implantation failure and miscarriage after IVF [68-69].

The rate of aneuploidy increases with increasing maternal age, which explains why advanced-age women have lower pregnancy rates and higher miscarriage rates in an IVF cycle utilizing unselected embryos. PGD and PGS allow for the identification of euploid, BRCA negative embryos which can be preserved through vitrification for future attempts at pregnancy. By understanding the female-age association to aneuploidy, couples committed to undergoing PGD to prevent BRCA transmission to their offspring should pursue fertility preservation treatment as early as possible to maximize euploid embryo yield. This strategy creates the most flexible plan to build a healthy family.

PGD allows for the selection and transfer of unaffected embryos. However, clinical and moral dilemmas arise when all the embryos are affected with the BRCA mutation or are indeterminate. In situations when the couple only has affected embryos, some couples may elect not to transfer, if the concern for future offspring with BRCA outweighs the desire for biological children. Others may consider transfer of only male embryos, with the knowledge that males are less likely to develop cancer as compared to females. One couple reported that the process of PGD only strengthened their desire to become parents, and elected to conceive naturally when presented with all affected embryos [58]. A case report of a patient who requested to transfer embryos of indeterminate status concluded that although this practice challenges the physician's duty to non-maleficence and social justice, transferring BRCA affected embryos was ethically permissible with adequate counseling [70]. In these circumstances, individualized care may be dictated by patient autonomy and guided by careful counseling with a geneticist and institutional ethics committees.

### Risks of Controlled Ovarian Hyperstimulation in BRCA

#### Carriers

Women without a BRCA mutation are not more likely to develop breast cancer after the use of ART treatment. Zreik et al. performed a meta-analysis summarizing the results of 8 cohort and 15 case-control studies that examined the risk of breast cancer in patients taking fertility medications. They found no significant increased risk of breast cancer after taking both clomiphene citrate (RR 1.08 95% CI 0.98-1.19) and composite gonadotropins (RR 0.99 (95% CI 0.89-1.11)). Furthermore, they found no significant risk of breast cancer associated with the number of completed treatment cycles (RR 1.08 (CI 0.92-1.26)) [71]. Belt-Dusebout et al. assessed the long-term risk of breast cancer after ovarian stimulation and observed that after a median follow up of 21 years, breast cancer risk in IVF-treated women was still not statistically different from that in the general population (standardized incidence ratio 1.01 [95% CI, 0.93-1.09]) [72].

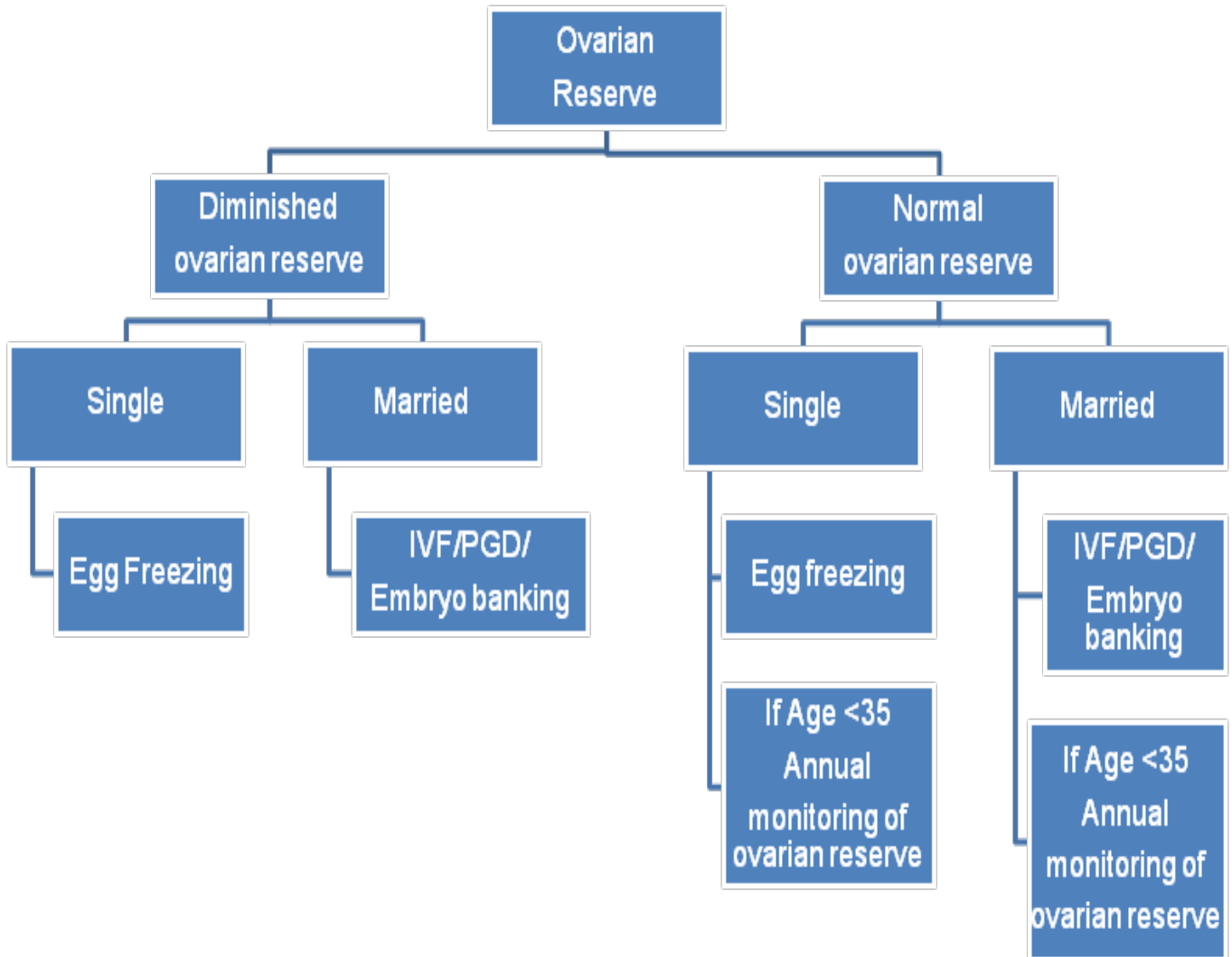


Figure 1: Options for BRCA carriers who plan to utilize PGD

This algorithm may be used to manage fertility preservation options for BRCA carriers who plan to use PGD to identify affected embryos and avoid transfer of BRCA mutation to offspring.

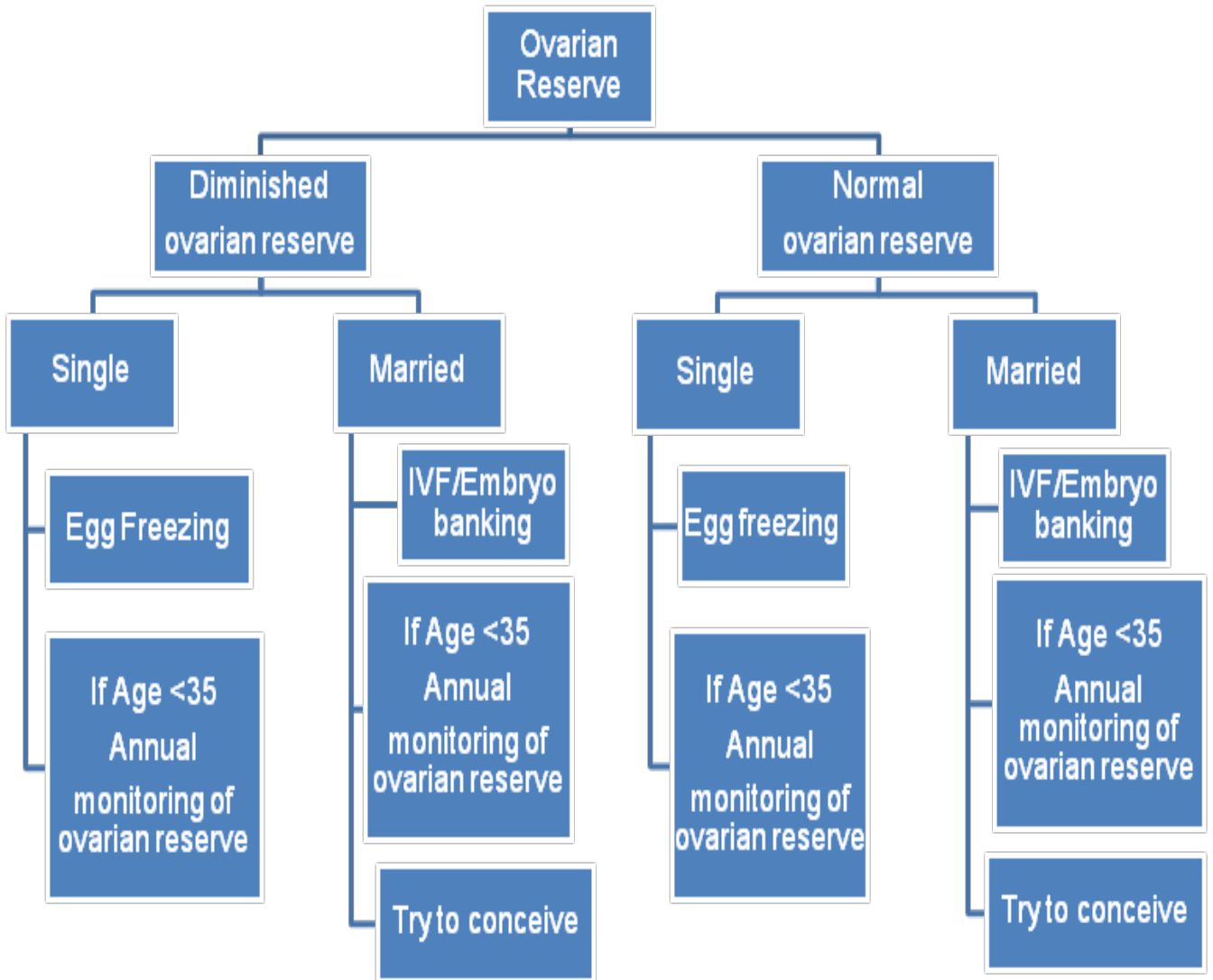


Figure 2: Options for BRCA carriers who do not plan to utilize PGD

This algorithm may be used to manage fertility preservation options for BRCA carriers who elect not to utilize PGD.

BRCA carriers are predisposed to increased risk of developing breast cancer, but current literature does not demonstrate that undergoing COH further increases this risk. Kotsopoulos et al. conducted a matched case-control study of 1,380 pairs of women and found that BRCA carriers who had used fertility medications were not at increased risk of breast cancer (OR 1.21, 95% CI 0.81-1.82) compared to non-users [73]. A study of 337 women with breast cancer by Kim et al. compared outcomes of patients who underwent COH with co-administration of gonadotropins and letrozole prior to breast cancer treatment compared to patients who did not undergo any fertility preservation procedure and found no increased risk of recurrence after five years of follow-up and no effect on survival outcomes of BRCA carriers [74].

Previous studies have also examined the effect of fertility treatments on subsequent ovarian cancer risk within the general population. Rizzuto et al. performed a meta-analysis including 11 case control and 14 cohort studies and reported no increased incidence of invasive ovarian cancer among women undergoing ART treatment with any fertility medication [75]. These findings agreed with an earlier cohort of over 2,400 Israeli women who were followed for >30 years after exposure to infertility medication [76]. Previous studies that reported a positive association between infertility treatment and invasive ovarian cancer were limited by small sample sizes, imprecise drug exposure information and treatment indication, and short term follow up [77-79].

The risk of ovarian cancer in BRCA carriers undergoing infertility treatment is limited to two large studies. A study of 1073 Jewish Israeli BRCA carriers, 164 of whom received infertility treatment and 909 of whom did not, demonstrated that fertility treatment regardless of type of medication used was not associated with invasive epithelial ovarian cancer risk [80]. A matched case-control study of 941 pairs of BRCA1 and BRCA2 carriers similarly showed no significant relationship, regardless of type of fertility medication, between both IVF/IUI and ovarian cancer risk [81].

The literature does suggest that women with infertility in the general population are at higher risk of having ovarian borderline tumors. The first meta-analysis to independently assess the risk of borderline tumors comprised twelve case control studies and showed a four-fold increased risk associated with infertility treatment. These findings have been supported by numerous subsequent studies including a pooled analysis of 8 case-control studies by Ness et al. and a cohort of 19,000 IVF patients by Leeuwen et al [82-85]. Therefore, infertility diagnosed from DOR may be a sign or symptom of underlying, preexisting borderline tumors. Furthermore, the absolute risk of borderline tumors remains low as the baseline risk of borderline tumors is 0.2% in the general population. [86]. To our knowledge there are no studies specifically assessing the risk of borderline tumors in BRCA patients undergoing COH.

## Conclusion

BRCA carriers are at a higher risk of developing both breast and ovarian cancer, and at a young age, and therefore require vigilant screening to prevent cancer-associated morbidity and mortality. The National Cancer Comprehensive Network recommends a risk-reducing BSO between ages 35 and 40 or after the completion of childbearing. Since many women have not completed childbearing by age 40, they have the option of undergoing fertility preservation with either oocyte or embryo cryopreservation prior to undergoing this risk-reducing surgery. PGD is a modern technique that may be employed with embryo cryopreservation to assist in the selection of embryos without a BRCA mutation, which could avoid the propagation of BRCA1 and/or BRCA2 to future offspring. Many studies continue to demonstrate ART treatment to be safe in BRCA carriers. Any association to fertility and BRCA carrier status remains conflicting in the reproductive community. Some studies suggest BRCA carriers may have decreased ovarian reserve compared with the general population, an effect that may be more pronounced in carriers of the BRCA1 mutation. However, others have failed to confirm this association.

BRCA carriers are faced with complex challenges and need health care professionals to discuss not only the medical implications of their carrier status and risk-reducing options, but to also share information regarding fertility preservation and the use of PGD to prevent transmission to their offspring. It is important for BRCA carriers to know that there are ways they can safely build a family. Patients are advised to meet with a reproductive specialist as early as possible, especially since advanced maternal age remains a central concern to a patient's chance to achieve a successful pregnancy.

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