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FERTILITY ISSUES TO DISCUSS WITH WOMEN CARRYING A BRCA1/2 MUTATION

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Abstract – *Women with BRCA1 or BRCA2 genes mutations could have an increased risk of prematurely impaired fertility and premature ovarian failure. Theoretically, several patho-physiological hypotheses support this finding, as well as the involvement of the BRCA genes in maintaining telomere length and the DNA repair anomalies promoting oocyte apoptosis. Advance of age at menopause and poorer response to ovarian stimulation have also been observed, but data on the increased risk of infertility remain weak and questionable.*

Furthermore, the high risk for breast and tubo-ovarian cancers increase the risk of infertility, due to surgery, to the ovarian toxicity of chemotherapy, to the long duration of hormone therapy when indicated, and to the waiting time advised before pregnancy. Current fertility preservation techniques have limitations, some of them being specific to BRCA1/2 women: the oncological risk due to stimulation in BRCA1/2 women has not been completely investigated and ovarian cortical transplantation might not be suitable for the high risk of developing ovarian cancer. Some key points about fertility are reviewed in this article to help clinicians discussing these issues with patients carrying a BRCA1/2 mutation.

KEYWORDS: *BRCA, Breast cancer, Ovarian cancer, Fertility, Fertility preservation, Counseling.*

BACKGROUND

Women who are BRCA1/2 mutation carriers have an estimated 40–85% lifetime risk of developing breast cancer and 16-64% risk of ovarian cancer. *BRCA* mutations may be associated with excess DNA errors in oocytes leading to a smaller oocyte reserve, occult primary ovarian insufficiency, and decreased fertility[1].

Thus, BRCA1/2 mutation carriers could have a lower ovarian reserve than the general population, exposing them to a higher risk of infertility, regardless of the occurrence of cancer. Theoretically, several patho-physiological hypotheses support this finding, as the involvement of the BRCA genes in maintaining telomere length, the DNA repair anomalies promoting oocyte apoptosis and differences in FMR1 (fragile X mental retardation 1) genotype. Advance of the age at menopause and poorer response to ovarian stimulation have been observed, but data on the increased risk of infertility remain weak and questionable.

The potential risk of premature ovarian failure and the high prevalence of cancer at an early age make discussion about fertility issues in BRCA1/2 mutation carriers as important as in young cancer patient[2].

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To review the association between BRCA1 and/or BRCA2 mutations and fertility issues, we interrogated PubMed Database using the following strategy: ((((hereditary [tiab] OR brca1 [TIAB] OR brca2 [TIAB] OR Genes, BRCA1 [MH] OR Genes, BRCA2 [MH]) AND (cancer [tiAB] OR neoplasms [mh])) OR "Neoplastic Syndromes, Hereditary" [Mesh]) AND (Primary Ovarian Insufficiency [mh] OR fertility [mh] OR infertility [mh] OR infertil* [tiab] OR fertility [tiab] OR PREGNANCY RATE[MH] OR "Reproductive Physiological Processes/statistics and numerical data" [Mesh] OR fertility preservation [MH]) AND (female OR women OR woman)) NOT male [ti].

The main key points to discuss with patients are summarized in table 1 and discussed in detail in the following paragraphs.

BRCA1/2 MUTATIONS SEEM TO BE AS FERTILE AS NON-CARRIERS

The proportion of infertility was reported similar (14.4% *vs.* 14.1%, $p = 0.81$) in a study that compared 2254 *BRCA1/2* mutation carriers to 764 comparable non-carriers[3].

The proportion of women reporting a fertility disorder was not significantly different (12.5% *vs.* 13.7%, $p = 0.46$) between BRCA mutated groups and controls in the Canadian case-control study by Finch[4].

No significant differences in terms of parity, age at first pregnancy, or use of infertility treatments where found in a case-control study comparing patients carrying *BRCA1* or *BRCA2* mutations compared to non-affected controls[5].

No significant differences in terms of fertility and average number of pregnancies were reported in carriers versus non-carriers in a study including 260 Ashkenazi Jewish patients treated for ovarian cancer (including 96 *BRCA* mutation carriers and 164 non-carriers) and 331 Ashkenazi Jewish women with no history of ovarian cancer[6]. However, the pregnancy rate was significantly lower in patients who have had ovarian cancer and the association between infertility and risk of ovarian cancer has been well described in the general population.

BRCA carriers had significantly more pregnancies completed, a shorter interval between pregnancies and higher average age at last pregnancy when 42 *BRCA1/2* mutation carriers born before 1930 were compared to 630 control women. These data come from records of Utah's population with knowledge of the *BRCA* statutes (mandatory Carriers) to observe fertility by "natural condition"[7].

Another study too seemed to paradoxically suggest a better fertility in women (and men) with *BRCA1/2* mutation[8]. This study included 2168 families, 1775 families without identified mutation, 214 families with *BRCA1 mutation,* and 161 families with *BRCA2 mutation, summing up to a total of 96,325 individuals.* In families with identified mutations, the proportion of childless women was significantly lower (9.1% *vs.* 16.0%, $p = 0.003$), and the average number of children significantly higher (1.8 per 1, 5, $p = 0.002$) compared to non-carriers within the same families. Compared to non-carriers from other families, the proportion of childless women was again significantly lower for mutation carriers (9.1% *vs.* 15.7%, $p = 0.005$), but no significant difference was found in the number of children.

TABLE 1. Fertility issues to discuss with women carrying a BRCA 1/2 mutation.

BRCA1/2 mutations seem to be as fertile as non-carriers
BRCA carriers could have a normal response to ovarian stimulation
BRCA1 women seem to have a lower level of markers of ovarian reserve (AMH)
BRCA1/2 patients could have a premature menopause
Breast cancer risk in BRCA 1 mutation carriers decreases with increasing age at first birth
Among BRCA 2 carriers, increasing parity was associated with significant increase in premenopausal breast cancer risk
BRCA1/2 mutations increase the risk of early cancer risk, before parenthood
Chemotherapy seems to induce more amenorrhea and premature menopause in BRCA 2 carriers
BRCA1/2 mutation carriers with endocrine responsive breast cancers have an additional reproductive risk factor due to tamoxifen administration
BRCA1/2 mutation carriers are candidates for prophylactic oophorectomy which reduces the reproductive window
Ovarian cryopreservation could be done just before prophylactic oophorectomy in women in younger than 40 years
Systematic fertility preservation in BRCA patients is still under debate
Specific risks of ovarian stimulation are not well known and letrozole could be a good option
Cryopreservation of ovarian cortex is not safe in BRCA1/2 mutation carriers
In vitro oocyte maturation could be useful but it is still experimental
Prophylactic fimbriectomy is still an experimental but promising mean of reducing ovarian cancer risk, while mantaining ovarian function

The mechanisms linking BRCA1 and BRCA2 mutations to female fertility are not fully understood but factors affecting telomere integrity may play a key role. Telomere length declines with age in all mitotic tissues except germ line tissue. Disruption of BRCA1 may result in telomere lengthening and show that the over expression of BRCA1 limits telomerase activity and reduces telomere length. This seems to suggest that BRCA1 mutations protect telomeres[9,10], but this mechanism has not been confirmed[11].

Thus data do not suggest that infertility is associated with the presence of a BRCA1/2 mutation. The only paper reporting increased fertility in BRCA1/2 carriers was based on an historic population when family planning was not available and is hardly reproducible nowadays. The possible increased fertility could explain a reproductive advantage of BRCA mutation that counterbalances its oncologic effects. Nonetheless, different factors could explain the low population prevalence of BRCA1/2 mutation. One of these is the grandmother effect: grandmothers ordinarily would enhance the fertility of their daughters, but in the case of BRCA1 mutation carriers, their own excess mortality, being carriers with an elevated risk of adult mortality, would have limited this benefit, and low female reproduction in primitive societies could have created circumstances that selected against BRCA1/2 mutations[12,13]. In conclusion BRCA carriers should be reassured that their fertility seems to be the same as non-carriers, but warned that they better not wait too long before trying to conceive.

BRCA CARRIERS COULD HAVE A NORMAL RESPONSE TO OVARIAN STIMULATION

In a study of 8 BRCA1 mutation carriers, with 1 also having a BRCA2 mutation, and 4 BRCA2 carriers undergoing ovarian stimulation for fertility preservation before chemotherapy for breast cancer, the number of oocytes collected from the BRCA1 mutation carriers was significantly lower: 7.4 (95% CI, 3.1 to 17.7) against 12.4 (95% CI, 10.8 to 14.2; = 0.25)[14]. The stimulation involved FSH and letrozole. After adjustment for age, the risk of poor response (≤ 4 oocytes retrieved) was multiplied by 24.7 (95% CI = 1.9 to 208, $p = 0.003$). The subgroup analysis found a significant risk of poor response in case of BRCA1 mutation (OR = 38.3 (95% CI = 4.1 to 353.4), $p = 0.001$), but not for BRCA2 mutation carriers. However, the small numbers of this study led to caution in interpreting the data and were not confirmed in a recent study[15].

In this study[15] a total of 62 BRCA mutation carriers and 62 matched non-carriers were included; 42 were fertility preservation breast cancer patients, and 82 were PGD non-cancer patients. Mean (±SD) age of patients was 32 ± 3.58 years. Number of stimulation days and total stimulation dose were comparable between carriers and non-carriers. Their cycles resulted in comparable oocyte yield (13.75 *vs.* 14.75) and low response rates (8.06% *vs.* 6.45%). Number of zygotes, fertilization rates, and conception rates were also comparable. In conclusion, BRCA mutation carriers seemed to have a normal ovarian response in IVF cycles. Thus, the jury is still out on this issue.

BRCA1 WOMEN SEEM TO HAVE A LOWER LEVEL OF MARKERS OF OVARIAN RESERVE (AMH)

In a 2014 study, the risk of having a lowered Anti Mullerian Hormone (AMH) <1.0 ng/mL was increased in case of BRCA1 mutation (OR = 4.22 (95% CI = 1.48 to 12.0)[16]. The level of AMH was significantly lower in BRCA1 mutation carriers compared to control women (0.53 ng/mL (95% CI 0.33 to 0.77) *vs.* 1.05 ng/mL (0.76 to 1.40). There was no AMH difference between patients with BRCA2 mutation and control patients and no differences in terms of parity between the three groups in this cross-sectional study.

In a study of ovarian aging and repair system[17], the rate of AMH were described as significantly lower in BRCA1 (15 women BRCA1, $p < 0.0001$) but not among BRCA2 (9 women BRCA2, $p = 0.127$), compared to the rate of AMH in 60 women without BRCA mutation.

In a smaller study[18], no significant difference in the rate of AMH compared to controls was found and none of the 41 women with BRCA1/2 mutation had a history of infertility.

In the absence of infertility, the predictive value of AMH on the probability of obtaining a spontaneous pregnancy remains unclear[19].

The earlier decline in ovarian reserve in BRCA1 and BRCA2 carriers can be explained by the fact that BRCA1 and BRCA2 are two genes involved in the pathway of homologous recombination (HR), a major repair pathway of double strand breaks in DNA[20]. These could well play a role in maintaining telomere length which is associated with the duration of reproductive life[21].

On the other hand, the double-strand breaks are a normal phenomenon of meiosis to permit homologous recombination (HR) between chromosomes[22]. Anomalies of the HR repair system lead to oocytes apoptosis, resulting in ovarian reserve decline. Other

genes belonging to this repair pathway have been identified as predisposing to premature ovarian failure[23]. Fanconi anemia is sometimes connected to the bi-allelic altered BRCA2 (also called FANCD1) or PALB2 (also called FANCN). The ataxia telangiectasia syndrome is related to the bi-allelic mutation of ATM, an important gene involved in the HR pathway. The bi-allelic alteration of certain HR genes is known to induce premature ovarian failure[24]. An *in vitro* study in mouse ovaries and human oocytes seems to confirm this hypothesis[17] finding a significant reduction in ovarian expression of different genes of the HR pathway (BRCA1, RAD51, ATM, MRE11) during aging, although BRCA2 was not involved.

Another possible explanation comes from the comparison[25] of FMR1 (fragile X mental retardation 1) mutation carriers, BRCA1/2 mutation carriers and non-mutated women. FMR1 mutation is involved in the X fragile syndrome, and in case of permutation, depending on number of CGG triplet repeat in Xfra locus, in some premature ovarian failure (POF) cases. Differences in FMR1 genotypes have been described as being related to the risk of POF[26].

AMH should therefore be measured in BRCA carriers to assess a possible early exhaustion of ovarian reserve.

BRCA1/2 PATIENTS COULD HAVE A PREMATURE MENOPAUSE

Different studies looked at the age of spontaneous menopause in patients carrying a mutation of *BRCA1/2*, as a marker of ovarian reserve.

Among women with breast cancer, the average age of onset of menopause was significantly earlier in women mutated *BRCA1* (45.3 years) than in non-mutated women (48.2 years) *($p < 0.05$)* in a cohort study[27].

In a case-control study[4] the average age of onset of menopause (defined as at least one year amenorrhea) was significantly lower in mutated (49.0 *vs.* 50.3 years, $p = 0.001$), mostly in mutated *BRCA2* (50.8 *vs.* 49.2, $p = 0.006$). Twelve mutated women (4.7%) were menopausal before the age of 40, compared to 2 (1.4%) in the control group *($p = 0.04$)*. At the age of 50 years, 61.1% of mutated *BRCA1, 62.0% of mutated BRCA2* and 47.1% of non-mutated were postmenopausal *($p = 0.09$)*.

In a cross-sectional study[28], after adjustment for parity, smoking and oral contraception assumption, menopause (defined as at least one year amenorrhea) occurred significantly earlier in women with *BRCA1/2* mutation, with an Hazard Ratio (HR) of 3.98 (95% CI, 2.87 to 5.53, $p < 0.001$). Excluding iatrogenic (secondary to chemotherapy) and surgical menopause, the age of natural menopause remained significantly younger in *BRCA1/2* mutation carriers (49 *vs.* 53 years), $p < 0.0001$.

In another case-control study, the cumulative risk of earlier menopause was not significant for *BRCA1 mutation carriers* (*HR = 1.06 (95% CI = 0.79 to 1.44, $p = 0.7$)* nor for *BRCA2 carriers (HR = 1.01 (95%CI = 0.73 to 1.40; $p = 0.9$)*, compared to controls[5].

In this study, though, only 19% of patients had reached natural menopause, while a large proportion of cases were censored at the time of cancer occurrence, had prophylactic surgery, or used hormonal treatment. So the subject remains controversial: we can only tell patients that some controversial data suggest a higher risk of premature menopause in BRCA1/2 carriers.

BREAST CANCER RISK IN BRCA1 MUTATION CARRIERS DECREASES WITH INCREASING AGE AT FIRST BIRTH

Breast and ovarian-tubal cancer risk is reduced by early pregnancy, number of children and lactation in the general population[29].

Unfortunately, in BRCA1 mutation carriers, the breast cancer risk seems to be increased by early age at pregnancy. A meta-analysis[30] showed a decrease in the risk of breast cancer in BRCA1 mutation carriers with aging: women aged 30 years or older vs. women younger than 30 years (ES = 0.65; 95% CI = 0.42 to 0.99) and the same was shown for women aged 25 to 29 years versus those aged less than 25 years (ES = 0.69; 95% CI = 0.48 to 0.99). Breastfeeding is associated with reduced ovarian cancer risk in BRCA1 mutation carriers. Late age at first birth, breastfeeding, and late age at menarche protect against breast cancer in BRCA1 mutation carriers in another study[31].

This is inconsistent with the effect in the general population and can be explained by at least two hypotheses: 1) the effect of age at first birth is different in BRCA1 mutation carriers than in the general population, or 2) the use of risk-reducing oophorectomy or bias in ascertainment may have affected these results. Additional research is required to determine whether these or other explanations can be given for this result. In addition, no reproductive factor or any modifier was unequivocally associated with risk modification in BRCA2 mutation carriers in both of the cited studies.

The subject remains controversial and it is unwise to advise to postpone pregnancy in order to reduce breast cancer risk in BRCA1 carriers because it contrasts with their increased decline in ovarian reserve.

AMONG BRCA2 CARRIERS, INCREASING PARITY MIGHT BE ASSOCIATED WITH A SIGNIFICANT INCREASE IN PREMENOPAUSAL BREAST CANCER RISK

It is still controversial whether or not pregnancy reduces or increases breast cancer risk in women with *BRCA* mutations. A study[32] found that among BRCA1 carriers, parity per se was not associated with the risk of breast cancer (OR for parous *vs.* nulliparous is 0.94; 95% CI = 0.75-1.19; $p = 0.62$). However, women with a BRCA1 mutation and 4 or more children had a 38% decrease in breast cancer risk compared to nulliparous women (OR = 0.62; 95% CI = 0.41-0.94). In contrast, among BRCA2 carriers, increasing parity was associated with an increased risk of breast cancer; women with 2 or more children were at approximately 1.5 times the risk of breast cancer as nulliparous women (OR = 1.53; 95% CI = 1.01-2.32; $p = 0.05$). Among women with BRCA2 mutations and who were younger than 50 ad diagnosis, the (adjusted) risk of breast cancer increased by 17% with each additional birth (OR = 1.17; 95% CI = 1.01-1.36; $p = 0.03$). There was no significant increase in the risk of breast cancer among BRCA2 carriers older than 50 (OR for each additional birth is 0.97; 95% CI = 0.58-1.53; $p = 0.92$). In the 2-year period following a birth, the risk of breast cancer in a BRCA2 carrier was increased by 70% compared to nulliparous controls (OR = 1.70; 95% CI = 0.97-3.0). There was a much smaller increase in breast cancer risk among BRCA2 carriers whose last birth was 5 or more years in the past (OR = 1.24; 95% CI = 0.79-1.95). A modest reduction in risk of breast cancer was observed among BRCA1 carriers with 4 or more births. Among BRCA2 carriers, increasing parity was associated with a significant increase in the risk of breast cancer before age 50 and this increase was greatest in the 2-year period following a pregnancy. Even if these data are intriguing, it is still premature to advise BRCA2 and BRCA1 mutation carriers to reduce and to increase the number of pregnancies, respectively.

BRCA 1-2 MUTATIONS INCREASE THE RISK OF EARLY CANCER RISK, BEFORE PARENTHOOD

Patients with mutation of BRCA1 and BRCA2 have a cumulative risk of developing breast cancer up to age 70 of about 57% and 49% respectively. The cumulative risk for ovarian cancer is 40% and 18%, respectively. According to a meta-analysis[33], *a 20-years old woman with a deleterious mutation in BRCA1* has a 12% risk of developing breast cancer between 20 and 40 years and 10% between 30 and 40 years of age. The risk of ovarian cancer for the same BRCA1 carrier is estimated at 3.2% between 20 and 40 years. For a 20 years-old subject with a deleterious mutation in *BRCA2, the risk of developing breast cancer within her forties is 7.5% of which 6.6% between 30 and 40 years.* The ovarian cancer risk occurs much later, with only 0.7% risk between 20 and 40 years.

One of the features of breast cancers in women with BRCA1 and 2 mutations is their early occurrence, affecting women who have not yet completed their reproductive projects, and may face difficulties to conceive after treatment. The average age at first pregnancy continues to increase, thus, the probability that a woman at a given age has not yet fulfilled her reproductive wishes tends to increase. Every BRCA carries must be warned to try to conceive ideally as young as possible.

CHEMOTHERAPY SEEMS TO INDUCE MORE AMENORRHEA AND PREMATURE MENOPAUSE IN BRCA2 CARRIERS

Breast cancer treatments cause infertility. Chemotherapy reduces ovarian reserve depending on patient age and on dosage and there are data that this effect might be more pronounced in BRCA2 mutation carriers. This data come from a study[34] on the risk of chemotherapy-induced amenorrhea, defined as a persistent amenorrhea for more than 2 years, occurring within 2 years after the end of treatment. This very imperfect reflection of ovarian reserve was assessed in 1,426 *BRCA1/2* mutation carriers and compared to 100 non-carriers. There was no significant difference in the chemotherapy-induced amenorrhea proportion relative to age, between carriers and non-carriers ($p = 0.18$), even after exclusion of those taking tamoxifen. Amenorrhea was significantly more frequent in *BRCA2* mutation carriers compared to *BRCA1* mutation carriers (46.8% *vs.* 32.7%; $p < 0.001$), even after adjustment for age ($p < 0.001$). After excluding patients taking tamoxifen (most numerous among the *BRCA2: 41% vs. 16%), the likelihood of chemotherapy-induced amenorrhea remained significantly different (36.6% for BRCA2 vs.* 27.8 BRCA1; $p = 0.04$). The age of natural menopause among women who recovered ovarian function after treatment was 45.4 years for women with *BRCA* mutation versus 49.0 for controls, $p < 0.001$. The possibility of a higher risk of amenorrhea and anticipated menopause age should be discussed with BRCA breast cancer patients[35].

BRCA1/2 MUTATION CARRIERS WITH ENDOCRINE RESPONSIVE BREAST CANCERS HAVE AN ADDITIONAL REPRODUCTIVE RISK FACTOR DUE TO TAMOXIFEN ADMINISTRATION

Patients with hormone receptor positive breast tumors, although less common with BRCA1 mutation, have an indication for hormone therapy for at least 5 years to reduce the risk of recurrence and mortality. The continuation of hormone therapy up to 10 years in some cases allows a further reduction of recurrence and mortality, especially in the very long term[36]. The extension of hormone therapy comes at the cost of an advance of age and therefore a strong decline in fertility. A precautionary period of 3 months wash out is often recommended after tamoxifen treatment before seeking a pregnancy, resulting in a further decline of the window of opportunity for fertility.

BRCA1/2 MUTATION CARRIERS ARE CANDIDATES FOR PROPHYLACTIC OOPHORECTOMY WHICH REDUCES THE REPRODUCTIVE WINDOW

The recommendation of prophylactic oophorectomy, usually within the age of 40 depending on the type of mutation and family history, narrows the already critical reproductive window in these patients. The recommendation of prophylactic oophorectomy at age 40 for patients carrying mutations of *BRCA1* can eventually change the parental project of these women. The recommendation of prophylactic oophorectomy is later for BRCA2 rather between 45 and 50, adapted by presence of family history of ovarian cancer. One in ten *patients carrying a mutation in BRCA1/2* in their twenties had their parental project modified by the recommendation of prophylactic oophorectomy[37].

This results in a further decline of window of opportunity for fertility.

OVARIAN CRYOPRESERVATION COULD BE DONE JUST BEFORE PROPHYLACTIC OOPHORECTOMY IN WOMEN YOUNGER THAN 40 YEARS

BRCA carriers, mostly if BRCA1 as their risk is higher, have a prophylactic oophorectomy recommendation at 40 years[38]. It does not seem licit to propose an ovarian cryopreservation so late at this age because the ovarian reserve and quality is low. In contrast, an oocyte preservation technique may be discussed in the rare cases when a prophylactic oophorectomy is envisaged earlier than 40 years old: in case of ovarian cancer family history of age 45 for example.

SYSTEMATIC FERTILITY PRESERVATION IN BRCA PATIENTS IS STILL UNDER DEBATE

As the oncological risk before age 40 for BRCA carriers is not negligible, this should be a reason to at least discuss fertility preservation with each woman harboring a BRCA mutation. After prophylactic mastectomy, the risk of breast cancer is low and that reduces the indication of fertility preservation. So the question of a systematic preservation of fertility in these patients, even before the onset of cancer, is controversial[39]. Around 90% of carriers will not have a breast cancer during the fertile period while there are some specific limitations or controversial points:

1) The relatively paucity of data about the safety of ovarian stimulation in BRCA1/2 mutation carriers;
2) The caveats about grafting ovarian cortex in patients at high ovarian cancer risk[40].

In conclusion, every BRCA mutation carrier should discuss about benefits and risks of prophylactic fertility preservation, even if some questions remain open.

SPECIFIC RISKS OF OVARIAN STIMULATION ARE NOT WELL KNOWN AND LETROZOLE COULD BE A GOOD OPTION

In theory, ovarian stimulation followed by oocyte or embryo vitrification should be performed prior to a significant decrease of ovarian reserve and possibly outside the urgent need for care of breast cancer, in order to maximize its efficacy[41]. The probability of pregnancy by each recovered oocyte is estimated between 5 and 7%, this figure being dependent on the age of the patient (less likely with advanced age)[42] and the estimated number of oocyte retrieved per stimulation cycle is 11.8±8, the mean number of oocytes recovered by stimulation is sometimes insufficient. Accumulation of vitrified oocytes, by several successive cycles could be an option[43] but data on breast risks when repeated stimulations are used in BRCA1/2 mutation carriers are still limited. Only one case-control study[44] examined this question and no excess risk was found, but only 20 mutation carriers underwent ovarian stimulation.

A recent study of 1073 *BRCA1/2* mutations carriers *in* which 164 women had received treatment

for infertility, compared the risk of ovarian cancer occurrence according to previous treatment for infertility[45]. In univariate and multivariate analysis, this study did not find any link between the use of treatment for infertility and the risk of ovarian cancer (OR = 0.63, 95% CI = 0.38 to 1.05), and regardless of the treatment used: clomiphene citrate, gonadotropins, or IVF. Nonetheless, the low number of patients in these studies leaves the question about safety of ovarian stimulation open.

If ovarian stimulation is performed, a comprehensive breast assessment, including MRI, breast ultrasound ± mammography, should be suggested for all women over 30 years. Moreover, short-term complications should be taken into account for BRCA1/2 mutation carrier. If stimulation followed by oocyte pick-up, the risk of severe complications with potential deleterious effect on future fertility, is about 0.7%. The risk of minor complication, with potential risk to delay treatment of breast cancer, is in the order of 8.5%[46].

Ovarian stimulation with letrozole appears to be an effective and relatively safe approach in women with breast cancer too, pending long-term follow-up, with results in pregnancy rates comparable with those seen with standard IVF treatments[47-49].

In conclusion, specific risks of ovarian stimulation in BRCA mutants are not well known, but patients must be informed and letrozole could be a good ovulation induction option.

CRYOPRESERVATION OF OVARIAN CORTEX IS NOT SAFE IN BRCA

Cryopreservation of ovarian cortex does not appear suitable in BRCA patients, given the risk of tubo-ovarian cancer in patients harboring a *BRCA1/2* mutation. Furthermore, the hypothetical decrease of ovarian reserve after this procedure should be considered[50] to minimize concerns regarding the development of ovarian cancer, an approach could be to transplant ovaries subcutaneously, but this strategy is purely speculative.

In conclusion, ovarian cortex cryopreservation does not seem appropriate for BRCA carriers and it is still experimental.

IN VITRO OOCYTE MATURATION COULD BE USEFUL BUT IT IS STILL EXPERIMENTAL

*In vitro oocyte m*aturation could be useful for *BRCA1/2* mutation carriers because it avoids ovarian stimulation, but the results in terms of pregnancy are still unknown[51].

PROPHYLACTIC FIMBRIECTOMY IS A STILL EXPERIMENTAL BUT PROMISING MEAN OF REDUCING OVARIAN CANCER RISK, WHILE MANTAINING OVARIAN FUNCTION

The technique of prophylactic fimbriectomy[52] followed by a later oophorectomy, may in the future provide a promising temporary solution. The limits are the need of IVF techniques to achieve pregnancy, and the fact that its preventive efficacy is not demonstrated. Studies are ongoing.

CONCLUSIONS

Young women who carry a mutation of *BRCA1/2* need intensive screening, they face difficult choices for preventive surgery and many will need tumor management at an early age. Furthermore they need a specific reproductive counseling, as they have some fertility differences compared with non-carriers. This is difficult because data on the alteration of fertility and ovarian reserve status *are still limited and controversial. This could add anxiety and uncertainties but still*, fertility issues should be discussed with them well *before the age of 30, when ovarian reserve allows good profitability for self-preservation techniques.* This discussion should go through a clear and honest information about the limited information available of the precise risk of ovarian failure and the expected benefits in terms of pregnancy of a fertility preservation methods[53].

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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