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Letter from the Editors



Dear ISFP Newsletter Readers:

In this Newsletter of the ISFP, we present a current article on "**Fertility Considerations in BRCA Mutation Carriers**"

by Peer, Shapira, and Raanani. This information is addressed to a relatively large population of young women with BRCA mutation who frequently need fertility preservation treatments and ART. Mutations in the *BRCA1* or *BRCA2* genes are associated with significant risks for developing breast and ovarian cancer and on many cases cancer occurs during reproductive ages. BRCA carriers often experience a limited reproductive window, and it has been suggested that *BRCA* carriers, especially *BRCA1*, have reduced reproductive potential. This article describes the causes of a limited fertility window and argues with the claims of reduced ovarian reserve and egg quality in *BRCA* carriers. Different strategies used to preserve fertility, including cryopreservation of embryo, oocyte or ovarian tissue and gonadotropin-releasing hormone analogue co-treatment are also discussed.

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*Every woman deserves
the chance.*

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Fertility Considerations In BRCA Mutation Carriers

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A germline mutation in either the *BRCA1* or the *BRCA2* genes is the most significant known risk factor (other than gender and increasing age) for developing breast and ovarian cancer. Mutations in these genes are highly penetrant and confer a lifetime risk for developing breast cancer (BC) of 40–90% and up to a 60% lifetime risk for developing ovarian cancer [1-4].

Reproductive and fertility related issues have long been an imperative aspect in the clinical management of *BRCA* mutation carriers and become most relevant in the 2nd and 3rd decade of life. **BRCA carriers often experience a limited reproductive window**, due to a number of causes listed hereafter.

- The most proven method for the prevention of ovarian cancer in *BRCA* mutation carriers is the unequivocal recommendation for risk reduction salpingo-oophorectomy (RRSO), which has consistently demonstrated a dramatic reduction in the risk of developing ovarian and fallopian tube cancer by over 80–85% [5, 6]. RRSO performed before 40 years of age has been shown to reduce early onset BC risk by approximately 50% [5]. **RRSO is recommended between 35 and 40 years of age after completion of childbearing**, or as individualized based upon family history of the earliest onset case of ovarian cancer.
- For those unwilling to undergo RRSO due to early menopausal symptoms, **interval bilateral salpingectomy followed with oophorectomy could be offered** [7]. It should be emphasized that there is no actual data on risk reduction for ovarian cancer by salpingectomy alone without oophorectomy
- **BRCA carriers often present with an advanced stage malignancy, at an earlier age, characterized by aggressive histology.** *BRCA1*-associated tumors are more likely to have high histological grade and to be of triple negative (TN) or medullary subtypes [8, 9]. These factors have an impact on diagnosis and treatment decisions; young patients with high grade, endocrine unresponsive tumors are more likely to receive chemotherapy, which might negatively affect fertility.
- **Prior to chemotherapy, BRCA mutation carriers frequently undergo IVF cycles for fertility preservation** [10]. As mentioned before, *BRCA* carriers have a shorter reproductive window. This is mostly due to chemotherapy induced ovarian failure and the necessity to postpone conception attempts, once BC is diagnosed. But it is also relevant for healthy carriers, who are frequently preoccupied by the appropriate timing for RRSO. Therefore, *BRCA* mutation carriers turn to IVF for fertility preservation much more frequently.

- **IVF for PGD is sought by BRCA mutation carriers who wish to eliminate the mutation from future offspring** [11, 12].
BRCA couples primarily classify PGD and prenatal diagnosis as reproductive options based on the perceived severity of hereditary breast and/or ovarian cancer alongside the moral issues, consequently weighing PGD risks against the optional benefits of eliminating the mutation from their future offspring [13].
- **It has been suggested by several authors that BRCA mutation carriers, especially BRCA1, have reduced reproductive potential** [14-16].
However, this concept is highly controversial as we recently demonstrated when reviewing current literature on parity, age at menopause and AMH levels among BRCA carriers (table-1) [17]. In a recent study we have also shown preserved IVF performance among cancer and non-cancer BRCA mutation carriers, when compared to matched controls [18]. Carriers and non-carriers had similar 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. These findings further question the role of BRCA mutation in compromising reproductive capacity.

Taking into consideration all of the above-mentioned causes for which BRCA mutation carriers seek reproductive consultation, it is clear that IVF and fertility preservation treatments form an important element in the management of these young patients, even more so when cancer is diagnosed. Advances in reproductive medicine might provide some solutions for the challenges that BRCA mutation carrier present.

- **For healthy BRCA carriers, cryopreservation of embryos and oocytes may be highly relevant** since family-planning decisions are often affected by the explicit recommendation for RRSO. In such cases there are no urgent schedule constraints and several ART cycles can be completed until RRSO is performed.
- In the face of a newly diagnosed breast cancer disease, a window of 6-8 weeks commonly exists between surgery and initiation of chemotherapy. This usually enables completion of **at least one IVF cycle for the purpose of storing embryos/oocytes before chemotherapy**. With luteal or random start of COH IVF cycle can also be accomplished prior to neo adjuvant chemotherapy [19] but fewer oocytes are usually aspirated.
- In case **immediate neo adjuvant chemotherapy is indicated, ovarian tissue cryopreservation (OTCP) can also be offered**. As opposed to other fertility preservation measures, OTCP can be safely performed after 1-2 chemotherapy cycles with no delay in cancer treatment.
- OTCP to preserve fertility has proven to be successful [20-23]. However, it carries the **potential risk of reintroducing metastatic cells in the stored ovarian tissue** [24-27] once autotransplantation is performed. Up to date, no ovarian metastases have been identified in women with BC, though none of the studies address BRCA mutation carriers specifically and **no reports on autotransplantation in carriers have been published thus far**. The high risk of ovarian cancer for the carriers and the recommendation for RRSO **contraindicates ovarian tissue transplantation**, but for some patients, facing dire straits, a temporary transplantation to complete reproductive plans is a possibility. OTCP might also be useful in

the future if in-vitro follicular maturation becomes applicable.

- In addition to the above mentioned active fertility preservation measures, a **protective ovarian effect may be provided when using gonadotropin-releasing hormone (GnRH-a) during chemotherapy**. Multiple studies suggest GnRH-a reduces ovarian damage, but others have shown mixed results and lack data on pregnancy outcomes [28]. The recently published study Prevention of Early Menopause Study (POEMS) [29] evaluated the rate of premature ovarian insufficiency (POI) following chemotherapy treatment of hormone receptor negative early breast cancer, with or without Goserelin. Results were encouraging for the use of Goserelin for protection; only 8% suffered ovarian failure after 2y follow-up vs. 22% ($p=0.04$) and 21% achieved pregnancy vs. 11% ($p=0.03$). However, the OPTION phase III randomized trial [30] also assessed similar population and found no difference thus far; final data have not yet been published. Three recent meta-analyses found GnRH-a conveys a statistical reduction in the risk of POI [31-33] but there is lack of uniform chemotherapy regimens, follow-up duration, and POI definition.

Healthy and affected BRCA mutation carriers, undergoing controlled ovarian hyperstimulation (COH) for IVF or for fertility preservation, are constantly concerned regarding the hormonal treatment implications on disease progression.

- Although not based on direct studies, it has been implied that the hyper-estrogenic state associated with COH for IVF could propagate cancer cell proliferation. **Recent studies demonstrated no increased risks for BRCA carriers treated for infertility with regard to future breast [14] or ovarian cancer [34]**. Hence, healthy BRCA mutation carriers can undergo regular COH cycles without the need for special protection.
- **For BC patients**, in order to account for the possible E_2 deleterious effect, specially **tailored protocols using gonadotropins with aromatase inhibitors (Letrozole) [35, 36] (figure-1) or co-administration of Tamoxifen 20mg [37] (figure-2)** for COH are routinely used. This approach is only relevant for hormone receptor positive BRCA mutation carriers suffering from BC.
- It is assumed that utilizing Letrozole to reduce estrogen exposure will reduce future risk for BC. **There is no available data as to the maximal E_2 levels which will provide protection against breast cancer**, and some patients still display very high E_2 levels (>2500 pmol/L) even when treated with Letrozole. Furthermore a retrospective cohort analysis of 16 IVF units using COH with adjuvant Letrozole has shown a significantly lower yield of oocytes [38], with a high percentage of immature oocytes of up to 20 % [35].
- **We recommend using the conventional Long GnRH agonist or Short GnRH antagonist COH protocols with adjuvant Tamoxifen**. Tamoxifen acts as a competitive estrogen antagonist in breast tissue and has a proven role in prophylaxis and treatment of hormonal receptor positive breast cancer irrespective of the induced elevated serum E_2 levels [39, 40]. We have recently shown that following pituitary suppression with GnRH agonist or antagonist, Tamoxifen can be added for the purpose of E_2 protection, with a satisfactory outcome in terms of oocyte yield and embryos, with no increase in cancer recurrence or mortality (figure-2). Short GNRH Agonist protocol with Tamoxifen is NOT recommended since in our study it appeared to have resulted in extremely high E_2 levels.

Conclusion

BRCA mutation carriers present with a variety of reproductive issues. They experience a narrow reproductive window, commonly dictated by medical/surgical measures that are taken to prevent or treat malignancy when it occurs. It is advisable to offer embryo/oocyte cryopreservation for fertility preservation to BRCA mutation carriers. For BC patients with endocrine responsive tumors we recommend adding Tamoxifen to conventional COH protocols for protection. Although ovarian tissue autotransplantation contradicts the recommendation for early BSO, a transplantation of frozen stored tissue can be performed for a limited period for time. The tissue should be removed as soon as reproduction plans are completed. OTCP might also prove useful in the future if in-vitro follicular maturation becomes applicable. Individual family planning and appropriate reproductive consultation might offer BRCA carriers and BRCA cancer patients the opportunity to safely complete their family plans and reduce future risks for ovarian and breast cancer.

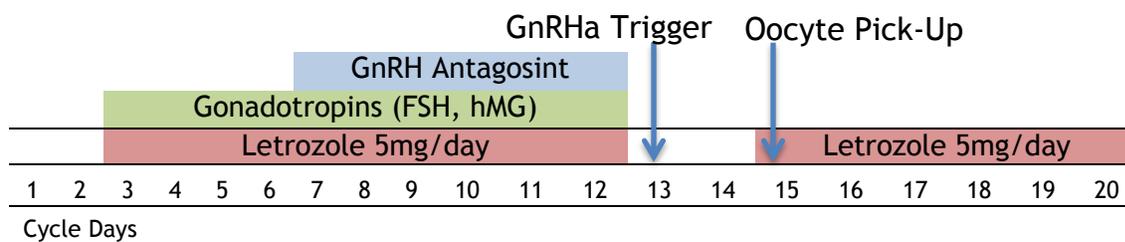
Table 1 - Reproductive performance in BRCA Mutation Carriers

Author	Number*	Patient Diagnosis	Endpoint	Results
<i>Comparable/Superior reproductive performance in BRCA mutation carriers</i>				
Pal et al.	2245	Breast Cancer, Non-Cancer	Parity Infertility Age at first birth	NS NS NS
Smith et al.	181	Non-Cancer	Parity	P=0.01
Finch et al.	908	Non-Cancer	Parity Use of infertility drugs Fertility Problems	NS NS NS
Collins et al.	829	Non-Cancer	Age at menopause	NS
Valenini et al.	1426	Breast Cancer	Risk for amenorrhea post chemotherapy	NS
Michelson-Cohen et al.	43	Non-Cancer	AMH Levels	NS
Van Tilborg et al.	1236	Breast Cancer, Non Cancer	Age at menopause	NS
Verpoest et al.	13	Non-Cancer	IVF performance	NS
<i>Diminished reproductive performance in BRCA mutation carriers</i>				
Rzepka-Górska et al.	39	Breast Cancer	Age at menopause	P<0.05
Oktay et al.	12	Breast Cancer	IVF Performance	P=0.001
Lin et al.	382	Non-Cancer	Age at menopause	P=0.01
Finch et al.	908	Non-Cancer	Age at menopause	P=0.001
Titus et al.	24	Breast Cancer	AMH Levels	P<0.0001
Wang et al.	143	Non-Cancer	AMH Levels	P<0.012

* Number of BRCA 1/2 mutation carriers included in study

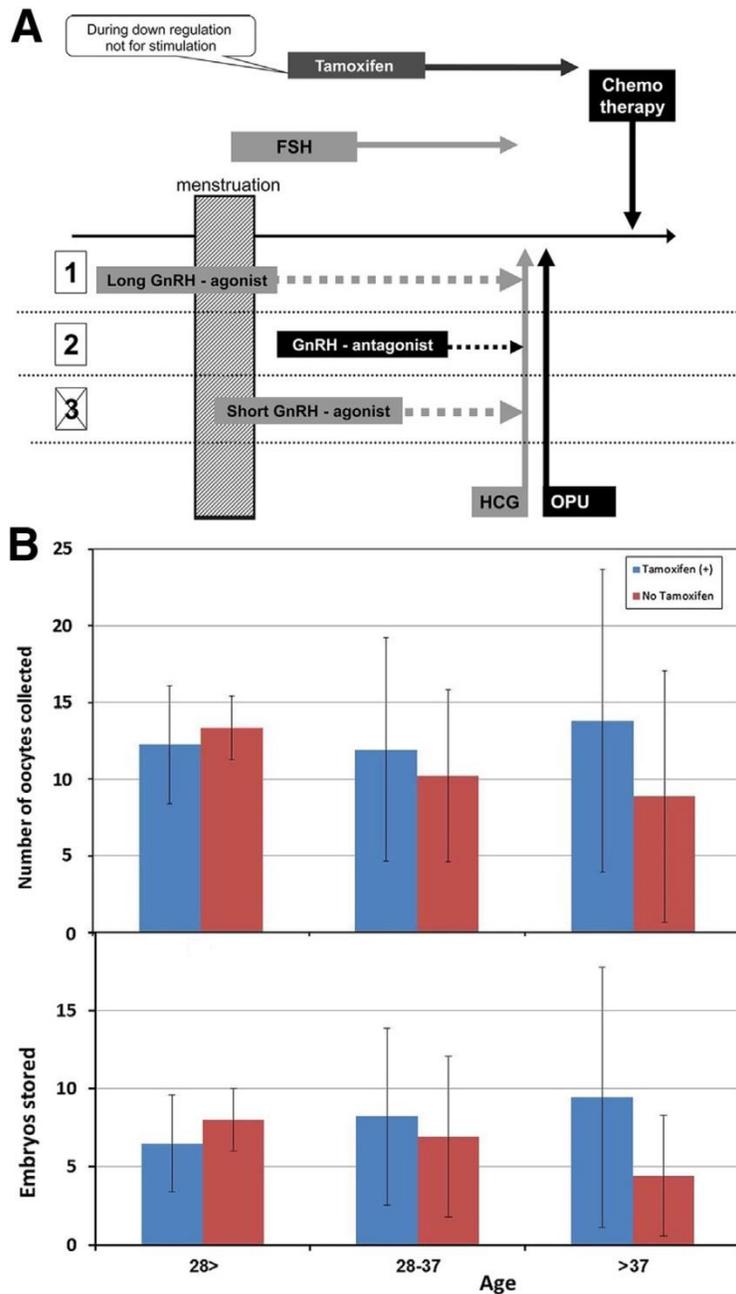
Shapira, M. et al *IVF for fertility preservation in breast cancer patients-efficacy and safety issues*. J Assist Reprod Genetics [17]

Figure-1 Ovarian Stimulation with Letrozole Supplementation and GnRH-a trigger



Rodriguez-Wallberg, K.A. and K. Oktay, Clin Obstet Gynecol, 2010. 53(4): p. 753-62[35]

Figure-2 Outcome of fertility-preservation cycles in breast cancer patients.



(A) Long luteal GnRH-a (1), and antagonist protocol (2), were used in this study; Short GnRH-a protocol (3) was not.

(B) COH protocols with or without Tamoxifen. Figure shows values \pm standard deviation.

Meirow, D., et al., *Fertil Steril*, 2014. **102**(2): p. 488-495 e3[37]

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Newsletter Submissions

Instructions for submissions

Deadline for Submissions : The 1st of the month prior to the next issue: (December 1, March 1, June 1 and September 1).

Submissions: ≤ 6 pages, double-spaced; consist of a concise summary of new findings and future directions; avoid extensive review of past literature; include relevant peer-reviewed references. Submissions will be reviewed by the President of the ISFP and the Editor for content and accuracy.

Editorials: ≤ 2 pages, double-spaced; clear statement of position and sources to support this position; employ insight, diplomacy and respect; inflammatory statements will not be allowed.

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