Gynecologic Oncology 186 (2024) 176–181

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Walking the tightrope: Fertility preservation among hereditary breast and ovarian Cancer syndrome Previvors

Sharonne Holtzman [a,*], Lily McCarthy [a], Samantha L. Estevez [a,b], Joseph A. Lee [b], Morgan F. Baird [b], Dmitry Gounko [b], Alan B. Copperman [a,b], Stephanie V. Blank [a]

[a] Icahn School of Medicine at the Mount Sinai Department of Obstetrics, Gynecology, and Reproductive Science, New York, NY, USA
[b] Reproductive Medicine Associates of New York, New York, NY, USA

HIGHLIGHTS

- Patients with Hereditary Breast and Ovarian Cancer Syndrome did not undergo expedited fertility treatment.
- Patients with BRCA1 presented for fertility consultation at an earlier age and had more oocytes retrieved during oocyte cryopreservation.
- Cycle outcomes did not differ in patients with Hereditary Breast and Ovarian Cancer Syndrome.

ARTICLE INFO

Article history:
Received 3 January 2024
Received in revised form 21 March 2024
Accepted 26 March 2024
Available online xxxx

Keywords:
Previvors
Hereditary breast and ovarian Cancer syndrome
BRCA

ABSTRACT

Introduction. Fertility-related concerns cause significant anxiety among patients with Hereditary Breast and Ovarian Cancer Syndrome (HBOC). The Society of Gynecologic Oncology and the American Society for Reproductive Medicine recommend patients diagnosed with HBOC receive early referral to a reproductive endocrinologist. However, evidence about fertility trends in this patient population are limited and guidelines are scarce. The aim of this study is to compare fertility preservation among patients with HBOC to control patients undergoing fertility treatment without a diagnosis of infertility.

Methods. This retrospective study included patients who presented to a single academic institution for fertility preservation in the setting of diagnosis of HBOC. In this study, HBOC patients are referred to as those who had tested positive for pathogenic mutations in BRCA1, BRCA2 or were at high-risk for HBOC based on a strong family history (defined as >3 family members diagnosed with HBOC) without a genetic mutation. HBOC patients were matched in a 1:1 fashion to a control group undergoing fertility preservation without a diagnosis of infertility or HBOC. All analysis was done using SPSS version 9.4 (SAS Institute, Cary, NC).

Results. Between August 1st, 2016 and August 1st, 2022, 81 patients presented to the study center for consultation in the setting of HBOC. Of those who presented, 48 (59.2%) ultimately underwent oocyte cryopreservation and 33 (40.7%) underwent embryo cryopreservation. Patients who underwent oocyte cryopreservation due to BRCA1 status were more likely to present for fertility consultation at a younger age compared to control patients (32.6 vs. 34.7 years, $p = 0.03$) and were more likely to undergo oocyte cryopreservation at a younger age (32.1 vs. 34.6 years, $p = 0.007$). There was no difference in age at initial consultation or age at procedure for patients with BRCA2 or patients with a strong family history compared to control patients ($p > 0.05$). There was no difference in the mean age of patients with HBOC at presentation for consultation for embryo cryopreservation or the mean age the patient with HBOC underwent embryo cryopreservation compared to control patients ($p > 0.05$). Patients with BRCA1 or BRCA2 did not have expedited time from consultation to first cycle start ($p > 0.05$). After adjusting for factors including anti-Müllerian hormone (AMH) level and age, patients considered in the HBOC group due to family history had less time between consultation and oocyte cryopreservation cycle compared to control patients. (179 vs. 317 days, $p = 0.045$). There was no difference in time from consultation to starting cycle for embryo cryopreservation for patients with HBOC compared to controls ($p > 0.05$).

Conclusion. Patients with HBOC did not undergo expedited fertility treatment compared to control patients undergoing oocyte and embryo cryopreservation for non-infertility reasons. Patients diagnosed with BRCA1 had more oocytes retrieved compared to the control population which is possibly due to earlier age of presentation in the setting of recommended age of risk reducing surgery being age 35–40. When age matched, cycle

* Corresponding author.
E-mail address: Sharonne.Holtzman@mountsinai.org (S. Holtzman).

https://doi.org/10.1016/j.ygyno.2024.03.025
0090-8258/

outcomes did not differ between HBOC and control patients. Given the known cancer prevention benefit and recommendations for risk-reducing surgery, future studies should focus on guidelines for fertility preservation for patients with HBOC.

1. Introduction

A previvor is defined as an individual who has an elevated predisposition to cancer without a diagnosis of cancer and was originally coined by Facing Our Risk of Cancer Empowered (FORCE) community member in 2000 on a message board [1]. Hereditary breast and ovarian cancer (HBOC) syndrome is characterized by multiple family members with breast and/or ovarian cancer, the coexistence of breast cancer and ovarian cancer in a single individual, and/or an earlier age of cancer diagnosis [3]. HBOC accounts for 5–10% of all breast and ovarian cancers [2]. The elevated risk of developing one or both cancers in HBOC is most frequently due to germline mutations in the BRCA1 or BRCA2 genes but may also be due to other more rare hereditary syndromes [4,5]. The care and treatment of women with HBOC is multifaceted and involves complicated risk-benefit analyses, conversations about optimal surveillance, preventative strategies, risk-reducing mastectomy and salpingo-oophorectomy, management of sexuality and menopause, and emotional support [6].

The current recommendations for management of patients with HBOC is to undergo risk-reducing surgeries that can impact fertility during childbearing years (ages 35–45) [7]. Because of this, fertility preservation is an area of great interest and clinical importance when caring for these patients. The Society of Gynecologic Oncology (SGO) and American Society for Reproductive Medicine (ASRM) recommend early referral of women with HBOC to reproductive endocrinologists for a fertility consultation [8–10]. Counseling women with HBOC on fertility-related issues is complex and necessitates a highly individualized approach to discussing topics including oocyte cryopreservation, embryo cryopreservation, in vitro fertilization (IVF), preimplantation genetic testing (PGT), and oocyte donation [11].

Despite the critical importance of fertility counseling and the possible subsequent clinical interventions for previvors, guidelines for fertility preservation in HBOC are limited [12,13]. There is widespread recognition that women with HBOC have unique concerns about their fertility and overall reproductive health [33,34]. To provide comprehensive care, these concerns warrant personalized consultation with reproductive endocrinologists, yet there is not any expert consensus on best approaches to advising and treating HBOC patients with fertility concerns [14–17]. Moreover, patients diagnosed with HBOC should be referred to a reproductive endocrinologist for a fertility consultation earlier than the general population. The aim of this study therefore was to compare fertility practices among HBOC patients to controls patients undergoing fertility preservation for non-infertility indications to provide data for counseling patients with HBOC on fertility preservation.

2. Methods

This retrospective, single academic center study included all patients diagnosed with HBOC or at high-risk based on family history who presented for fertility preservation from August 2016 to August 2022. This study was approved by the Institutional Review Board with a waiver of consent for retrospective analysis of de-identified data. Patients were included if they presented for fertility consultation in the setting of a documented pathogenic BRCA1 mutation, BRCA2 mutation, or had a strong family history (defined as >3 family members diagnosed with HBOC) without a known mutation. For the remainder of this manuscript, all patients who qualified for the investigational cohort will be identified as "HBOC patients." Exclusion criteria included any patient with minimal follow-up data, patients with a personal history of cancer, and patients who presented for a consultation without undergoing a fertility preservation procedure. Using natural language processing within the electronic medical record, the investigational cohort was identified using the following key words: BRCA, BRCA1, BRCA2, Hereditary Breast and Ovarian Cancer, and HBOC.

Once eligible patients were identified, a chart review was performed to obtain comparative demographic and clinical data. Demographic data collected included self-reported patient age, race, ethnicity and marital status. Clinical data collected included date of consultation, age at initial consultation, body mass index (BMI), date of fertility preservation procedure, age at the time of fertility preservation procedure, type of fertility preservation (oocyte vs. embryo cryopreservation), anti-Müllerian hormone (AMH) level, and the number of oocytes and embryos cryopreserved in the patients' first cycle. Included patients were divided into two investigational cohorts based on their fertility preservation procedure: Group 1 for oocyte cryopreservation and Group 2 for embryo cryopreservation. These two groups were then matched in 1:1 fashion to a control cohort undergoing fertility preservation for non-infertility reasons, no diagnosis of HBOC and no strong family history of breast or ovarian cancer. The patients were matched based on type of cryopreservation – egg or embryo and year procedure was done. Each group was also subdivided based on HBOC inclusion criteria as BRCA1, BRCA2, or high risk for further analysis.

Categorical data were reported as absolute frequencies and percentages. Comparative statistics for categorical variables were performed using non-parametric tests. Continuous variables were reported as means and analyzed by student *t*-test. Comparative statistics for continuous variables were performed using chi-square and Fisher's exact test, as appropriate. An adjusted logistic regression multivariate analysis was performed to evaluate the differences in patients' age at presentation, age at fertility preservation procedure, and time from consultation to procedure. In our multivariate analysis, AMH levels and age of patient was used in order to assess trends. All *p*-values were two-sided and were considered significant if <0.05. Statistical analysis was performed using the SPSS statistical program version 9.4 (SAS institute, Cary, NC).

3. Results

Between August 1st, 2016 and August 1st, 2022, 81 patients presented to the study center for reproductive endocrinology consultation in the setting of HBOC. Of those who presented, 48 (59.2%) underwent oocyte cryopreservation and 33 (40.7%) underwent embryo cryopreservation. There were no patients who underwent both oocyte or embryo cryopreservation.

3.1. Patient demographic data

For the control patients, the average age of consultation was 34.4 +/− 4.1 and the average age for embryo freezing was 35.5 +/− 6.7. The average number of oocytes retrieved for our control patients was 12.4 ±7.8.

When evaluating HBOC oocyte cryopreservation patients (Group 1), 14 (29.2%) had a history of BRCA1, 10 (20.8%) had a history of BRCA2, and 24 (50%) had a strong family history, as defined above. The mean

age at initial consultation within Group 1 was 33.8 years +/− 4.3, and at the time of oocyte cryopreservation procedure was 34.2 +/− 3.4 years. The majority of Group 1 patients, 37 (77.1%), were single. The mean AMH for this group was 2.58 ng/mL. Baseline demographics of Group 1 oocyte cryopreservation patients can be found in Table 1. Compared to control oocyte cryopreservation patients, HBOC patients who underwent oocyte cryopreservation due to BRCA1 status were more likely to present at a younger age (32.6 vs. 34.7 years, $p = 0.03$) and were more likely to undergo oocyte cryopreservation at a younger age (32.1 vs. 34.6 years, $p = 0.007$). There was no difference in age at initial consultation or age at procedure for patients with BRCA2 or patients with a strong family history compared to control patients ($p > 0.05$).

Among embryo cryopreservation HBOC patients (Group 2), 13 (39.4%) had a history of BRCA1, 7 (21.2%) had a history of BRCA2, and 14 (42.4%) had a strong family history. The mean age at initial consultation for all Group 2 patients was 32.6 years with a range. The mean age at the time of embryo cryopreservation procedure was 33.4 years +/− 5.3. The majority of Group 2 patients, 19 (57.6%), were married. The mean AMH level of 3.2 ng/mL. Baseline demographics of Group 2 embryo cryopreservation patients can be found in Table 2. There was no difference in the mean age of patients with HBOC who presented for consultation for embryo cryopreservation or the mean age of the patients with HBOC who underwent embryo cryopreservation compared to control patients ($p > 0.05$) Table 3.

3.2. Fertility preservation cycle outcome data

When evaluating oocyte cryopreservation cycle outcomes in Group 1, the mean number of oocytes that were retrieved in all patients undergoing oocyte cryopreservation 17.8. Within Group 1 HBOC subgroups the mean number of oocytes retrieved were as follows: 24.1 for BRCA1 patients, 17.2 BRCA2 patients, and 12.7 for patients with a strong family history. Compared to controls, BRCA1 patients were found to have a significantly higher number of oocytes retrieved (24.1 vs. 12.4, $p = 0.001$). There was no difference, however, in the mean number of oocytes retrieved in patients with BRCA2 or a strong family history when compared to controls ($p > 0.05$).

When evaluating embryo cryopreservation cycle outcomes in Group 2, the mean number of eggs retrieved for all HBOC patients was 20. Within group 2 HBOC subgroups the mean number of embryos were as follows: 22 for BRCA1 patients, 20 for BRCA 20 patients, and 19.5 for patients with a strong family history. Compared to control patients, there was no difference in the number of embryos in HBOC patients, ($p > 0.05$).

3.3. Time to initiation of care data

After adjusting for factors including AMH level and age, patients included in HBOC due to strong family history, however, did have less time between consultation and oocyte cryopreservation cycle compared to control patients (179 days vs. 317 days, $p = 0.045$). After adjusting for factors including AMH level and age, there was no difference in time from consultation to starting cycle for embryo cryopreservation for patients with HBOC compared to controls ($p > 0.05$).

4. Discussion

Previvors find themselves walking the tightrope as they balance fertility and cancer prevention concerns; they are “supposed” to take action on both during the same time period of life. Early referral to a reproductive endocrinologist has been recommended by SGO and ASRM, but in practice, what does that mean? Referrals are made, but who goes? Who follows through, and when? Are they freezing eggs or embryos? The aim of this study was to compare the fertility preservation-seeking practices and outcomes of patients with HBOC to controls, defined as people seeking fertility preservation for non-infertility indications. These findings can help us counsel our patients and guide them in shared decision making.

Table 1
Demographic information for all HBOC patients undergoing egg freezing ($n = 48$).

	All HBOC patients (n = 48)	BRCA 1 ($n = 14$)	BRCA2 ($n = 10$)	Family History ($n = 24$)	*P* Value
Average age at initial Consultation	33.8	32.6	33.6	34.7	$p = 0.7$
Average at at time of egg freezing procedure	34.2	33.1	34.1	35.1	$p = 0.3$
Race/ Ethnicity					$p = 0.42$
White	38 (79.2%)	10 (71.4%)	7 (70%)	21 (87.5%)	
Black	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Hispanic	2 (4.2%)	1 (7.14%)	1 (10%)	0 (0%)	
Asian	3 (6.3%)	1 (7.14%)	1 (10%)	1 (4.2%)	
Other	5 (10.4%)	2 (14.2%)	1 (10%)	2 (8.3%)	
Marital status					$p = 0.55$
Single	37 (77.1%)	11 (78.6%)	6 (60%)	20 (83.3%)	
Married	1 (2.1%)	0 (0%)	0 (0%)	1 (4.2%)	
Domestic partnership	4 (8.3%)	1 (7.14%)	2 (20%)	1 (4.2%)	
Divorced	2 (4.2%)	1 (7.14%)	0 (0%)	1 (4.2%)	
Not answered	3 (6.3%)	0 (0%)	2 (20%)	1 (4.2%)	
Average BMI	24.1	23.8	35.4	24.5	$p = 0.67$
Average AMH	2.58	2.87	3.26	2.09	$p = 0.33$
Gravidity					$p = 0.22$
0	45 (93.8%)	14 (100%)	10 (100%)	21(87.5%)	
1	3 (6.25%)	0 (0%)	0 (0%)	3 (12.5%)	
Alcohol Use					$p = 0.14$
Current	24 (50%)	8 (57.1%)	4 (40%)	12 (50%)	
Former	10 (20.8%)	1 (7.14%)	3 (30%)	6 (25%)	
Never	7 (14.6%)	4 (28.6%)	1 (10%)	2 (8.3%)	
Not answered	7 (14.6)	1 (7.14%)	2 (20%)	4 (16.7%)	
Smoking					$p = 0.09$
Current	2 (4.17%)	0 (0%)	0 (0%)	2 (8.3%)	
Former	2 (4.17%)	0 (0%)	0 (0%)	2 (8.3%)	
Never	28 (58.3%)	9 (64.2%)	6 (60%)	13 (54.2%)	
Not answered	16 (33.3%)	5 (35.7%)	4 (40%)	7 (29.2%)	

Table 2
Demographic information for all HBOC patients undergoing embryo freezing ($n = 33$).

	All HBOC patients (n = 33)	BRCA 1 ($n = 13$)	BRCA2 ($n = 7$)	Family History (n = 14)	P Value
Average age at initial Consultation	32.6	33.0	30.3	33.4	$p = 0.08$
Average age at time of embryo freezing procedure	33.4	34.0	30.9	34.5	$p = 0.34$
Race/ Ethnicity		10			$p = 0.12$
White	25 (77.6)	(77.0%)	7 (100%)	8 (57.1%)	
Black	1 (3.0%)	0 (0%)	0 (0%)	1 (7.1%)	
Hispanic	1 (3.0%)	1 (7.7%)	0 (0%)	0 (0%)	
Asian	4 (12.1%)	1 (7.7%)	0 (0%)	3 (21.4%)	
Other	1 (3.0%)	1 (7.7%)	0 (0%)	0 (0%)	
Marital status					$p = 0.43$
Single	8 (24.2%)	4 (30.7%)	0 (0%)	4 (28.6%)	
Married	19 (57.6%)	6 (46.2%)	6 (85.7%)	7 (50%)	
Domestic partnership	4 (12.1%)	2 (15.4%)	1 (14.3%)	1 (7.1%)	
Divorced	0 (0%)	0 (0%)	0 (0%)	0 (0)	
Not answered	3 (9.1%)	1 (7.7%)	0 (0%)	2 (14.3%)	
Average BMI	24.3	23.4	24.9	25.1	p = 0.34
Average AMH	3.2	3.2	1.74	3.8	$p = 0.92$
Gravity					$p = 0.07$
0	28 (84.8%)	10 (77.0%)	5 (71.4%)	13 (92.9%)	
1	5 (15.2%)	2 (14.5%)	2 (28.6%)	1 (7.1%)	
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
4	1 (3.0%)	1 (7.7%)	0 (0%)	0 (0%)	
Alcohol Use					$p = 0.21$
Current	16 (48.5%)	7 (53.8%)	4 (57.1%)	5 (35.7%)	
Former	8 (24.2%)	3 (23.1%)	3(42.9%)	2 (14.3%)	
Never	6 (18.2%)	1 (7.7%)	0 (0%)	5 (35.7%)	
Not answered	4 (12.1%)	2 (15.4%)	0 (0%)	2 (14.3%)	
Smoking					p = 0.14
Current	0(0%)	0 (0%)	0 (0%)	0 (0%)	
Former	2(6.1)	1 (7.7%)	0 (0%)	1 (7.1%)	
Never	22 (66.7%)	8 (61.5%)	7 (100%)	7 (50%)	
Not answered	10 (30.3%)	4 (30.8%)	0 (0%)	6 (42.9%	

In our cohort, BRCA1 patients were more likely to present for fertility consultation and undergo oocyte cryopreservation at a younger age compared to controls. Patients with BRCA2 and patients with strong family history did not seek consultation at an earlier age for oocyte preservation. For patients who had embryo cryopreservation, there was no difference in age of presentation in patients with HBOC compared to control patients. Given the early age of recommended risk reducing surgery for patients with HBOC and these surgeries' incompatibility with unassisted fertility, it is important to refer patients to a reproductive endocrinologist far in advance of these perceived deadlines to address fertility-related topics in an expedient manner [11].

Early referral of patients with HBOC and prompt counseling is especially important because fertility preservation strategies are most effective at younger ages [21–23]. Fertility counseling plays a crucial role for affected women as they make life-altering decisions about fertility related issues including timing of fertility and utilization of preimplantation genetic testing [20]. There are an increasing number of reproductive technologies and advancements to assist fertility for the previvor population including but not limited to, cryopreservation, donation of oocytes and embryos, gestational carriers, and adoption, that can enable women to preserve fertility or use alternative methods to build families [11]. Conversations about assisted reproductive technology treatment and other avenues to build families should be highly personalized and tailored to individual patients' specific genetic profiles, physical and emotional needs, and fertility-related goals requiring more nuanced fertility counseling and longer time for more decisions [24].

Another significant finding was that patients with BRCA1 mutations had a greater number of oocytes retrieved compared to control patients (24.1 vs. 12.4, $p = 0.001$). This finding is likely due to the younger age of consultation of the BRCA1 patients. Patients with BRCA1 were significantly younger at the time of oocyte cryopreservation compared to control patients whereas this was not the case for BRCA2 or family history. There is increasing awareness that patients with BRCA1 and BRCA2 mutations need gene-specific reproductive endocrinology consideration and counseling on future fertility given the unique genetic attributes of these two variants, but there is scant literature to date on ways in which fertility preservation may differ depending on BRCA subtype [30]. These findings provide insight into differences in fertility practices based on specific BRCA variants and add to the growing body of evidence related to women who fall into this particular category [32].

Patients with a strong family history of HBOC had a shorter time from consultation to starting cycle for oocyte or embryo

Table 3
Primary outcome for patients undergoing HBOC egg freezing vs controls (n = 48).

	All HBOC patients (n = 48)	BRCA 1 (n = 13)	BRCA2 (n = 7)	Family History (n = 14)	P Value
Age at initial consultation	33.8	32.6	33.6	34.7	**p = 0.03**
Age at egg freezing	34.2	33.1	34.1	35.1	**p = 0.007**
Median	16.6	23.4	14.8	13.5	**p = 0.001**
Number of eggs retrieved					
Time between presentation of consultation to start of cycle (days)	143.6	164.9	183.4	114.6	**p = 0.045**

cryopreservation compared to control patients. Patients with BRCA1 or BRCA2 did not undergo expedited oocyte or embryo cryopreservation. This result was somewhat surprising given that current clinical practice guidelines recommend that fertility be addressed as close to diagnosis as possible to provide patients with the maximum number of opportunities for fertility preservation [25]. A variety of factors may account for the lack of accelerated fertility treatment observed for HBOC patients. Albeit speculative, these may include delays due to practical concerns such as the complexity and cost associated with in vitro fertilization (IVF) procedures and the decision of pre-implementation genetics [24,26,27]. Few studies have evaluated differences in time to fertility treatment between HBOC patients and individuals without any such genetic diagnosis, as there is a scarcity of clinical data on fertility preservation in this population [28–30]. The lack of guidelines regarding optimal fertility preservation practices for different genetic pathologies may also help to explain the fact that there was no significant distinction in speed of fertility treatment for HBOC patients versus control patients in this study [31].

This study has several strengths, including one of the largest studies examining fertility concerns in HBOC, the longitudinal REI data and detailed clinical history. One of the principal limitations of this study is its retrospective design and the inherent nature of selection bias. There is potential for misclassification bias, as controls were not required to have had genetic testing, and could have been mutation carriers. Additionally, for the purposes of this study, patients with pathogenic mutations in other ovarian and breast cancer-associated genes were not included in the HBOC group. Another limitation is that we do not know what caused the delay in initiation of fertility consultation which may have been provider dependent or patient preference. A final limitation is related to the demographic characteristics of the cohort, specifically in terms of the breakdown of self-reported race/ethnicity for patients undergoing oocyte and embryo cryopreservation. A substantial percentage of these high-risk patients (71% undergoing oocyte cryopreservation and 79% undergoing embryo cryopreservation) identified themselves as white, which may also reduce the generalizability of the study results, as does the likely limited socioeconomic make up of the cohort. As more employers provide for these services and access increases, future patients with genetic predisposition to cancer seeking fertility preservation will hopefully be more diverse in every way.

In conclusion, patients with BRCA1 and BRCA2 did not experience expedited fertility treatment relative to the general population. These findings shed light on understudied fertility preservation dynamics in patients with HBOC. Future work will concentrate on expanding cohort size and heterogeneity in order to better characterize fertility patterns and best practices in this unique set of patients. Furthermore, fertility patterns in patients with genetic predisposition to cancer, including those with genetic mutations beyond BRCA 1 and 2, are still understudied and continue to pose significant challenges for both gynecologic oncology and reproductive endocrinology specialists [18,19]. Advancing technology, collaboration between the specialties and improving access to care will hopefully make this journey easier in the future for patients.

Disclosures

A portion of this project was presented at the BRCA 2023 symposium: Moving into the Mainstream in Montreal, Canada on May 2–5, 2023.

CRediT authorship contribution statement

Sharonne Holtzman: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Lily McCarthy:** Writing – review & editing, Writing – original draft, Investigation. **Samantha L. Estevez:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Joseph A. Lee:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Morgan F. Baird:** Data curation. **Dmitry Gounko:** Data curation. **Alan B. Copperman:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Stephanie V. Blank:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

No financial disclosures.

References

[1] S. Yang, J.E. Axilbund, E. O'Leary, S.T. Michalski, R. Evans, S.E. Lincoln, E.D. Esplin, R.L. Nussbaum, Underdiagnosis of hereditary breast and ovarian Cancer in Medicare patients: genetic testing criteria miss the mark, Ann. Surg. Oncol. 25 (10) (2018) 2925–2931, https://doi.org/10.1245/s10434-018-6621-4 Oct. Epub 2018 Jul 11. PMID: 29998407.

[2] ACOG Practice Bulletin No, 103: hereditary breast and ovarian cancer syndrome, Obstet. Gynecol. 113 (4) (2009) 957–966, https://doi.org/10.1097/AOG.0b013e3181a106d4 Apr. (PMID: 19305347).

[3] D.H. Marmolejo, M.Y.Z. Wong, S. Bajalica-Lagercrantz, M. Tischkowitz, J. Balmaña, Extended ERN-GENTURIS Thematic Group 3, Overview of hereditary breast and ovarian cancer (HBOC) guidelines across Europe, Eur. J. Med. Genet. 64 (12) (2021) 104350 Dec. doi: 10.1016/j.ejmg.2021.104350. Epub 2021 Oct 1. PMID: 34606975.

[4] D. Shao, S. Cheng, F. Guo, C. Zhu, Y. Yuan, K. Hu, Z. Wang, X. Meng, X. Jin, Y. Xiong, X. Chai, H. Li, Y. Zhang, H. Zhang, J. Liu, M. Ye, Prevalence of hereditary breast and ovarian cancer (HBOC) predisposition gene mutations among 882 HBOC high-risk Chinese individuals, Cancer Sci. 111 (2) (2020) 647–657, https://doi.org/10.1111/cas.14242 Feb. (Epub 2019 Dec 31. PMID: 31742824; PMCID: PMC7004523).

[5] M.M. AlHilli, P. Batur, K. Hurley, Z. Al-Hilli, D. Coombs, G. Schwarz, R. Djohan, J. Marquard, K. Ashton, H.J. Pederson, Comprehensive Care of Women with Genetic Predisposition to breast and ovarian Cancer, Mayo Clin. Proc. 98 (4) (2023) 597–609 Apr. 10.1016/j.mayocp.2023.01.001. Epub 2023 Mar 3. PMID: 36870859.

[6] M.M. AlHilli, H.J. Pederson, Controversies in hereditary Cancer management, Obstet. Gynecol. 137 (5) (2021) 941–955, https://doi.org/10.1097/AOG.0000000000004364 May 1. (PMID: 33831930).

[7] M.B. Daly, R. Pilarski, M.B. Yurgelun, M.P. Berry, S.S. Buys, P. Dickson, S.M. Domchek, A. Elkhanany, S. Friedman, J.E. Garber, M. Goggins, M.L. Hutton, S. Khan, C. Klein, W. Kohlmann, A.W. Kurian, C. Laronga, J.K. Litton, J.S. Mak, C.S. Menendez, S.D. Merajver, B.S. Norquist, K. Offit, T. Pal, H.J. Pederson, G. Reiser, K.M. Shannon, K. Visvanathan, J.N. Weitzel, M.J. Wick, K.B. Wisinski, M.A. Dwyer, S.D. Darlow, NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 1.2020, J. Natl. Compr. Cancer Netw. 18 (4) (2020 Apr) 380–391, https://doi.org/10.6004/jnccn.2020.0017 PMID: 32259785.

[8] S. Arab, T. Tulandi, W. Buckett, Hereditary breast cancer and fertility preservation outcomes, J. Assist. Reprod. Genet. 39 (5) (2022) 1163–1168, https://doi.org/10.1007/s10815-022-02486-0 May. (Epub 2022 Apr 11. PMID: 35403930; PMCID: PMC9107533).

[9] M. Jacobson, M. Bernardini, M.L. Sobel, R.H. Kim, J. McCuaig, L. Allen, No. 366-Gynaecologic Management of Hereditary Breast and Ovarian Cancer, J. Obstet. Gynaecol. Can. 40 (11) (2018) 1497–1510, https://doi.org/10.1016/j.jogc.2018.05.046 Nov. (PMID: 30473125).

[10] L.M. Chen, S.V. Blank, E. Burton, K. Glass, E. Penick, T. Woodard, Reproductive and Hormonal Considerations in Women at Increased Risk for Hereditary Gynecologic Cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine Evidence-Based Review, Gynecol. Oncol. 155 (3) (2019 Dec) 508–514, https://doi.org/10.1016/j.ygyno.2019.06.017 Epub 2019 Oct 9. Erratum in: Gynecol Oncol. 2020 Mar;156(3):748. PMID: 31606283.

[11] S. Paluch-Shimon, F. Cardoso, C. Sessa, J. Balmana, M.J. Cardoso, F. Gilbert, E. Senkus, ESMO Guidelines Committee, Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening, Ann. Oncol. 27 (Suppl. 5) (2016 Sep), https://doi.org/10.1093/annonc/mdw327 v103-v110. Erratum in: Ann Oncol. 2017 Jul 1;28(suppl_4):iv167-iv168. PMID: 27664246.

[12] G. Corrado, C. Marchetti, R. Trozzi, G. Scambia, A. Fagotti, Fertility preservation in patients with BRCA mutations or lynch syndrome, Int. J. Gynecol. Cancer 31 (3) (2021) 332–338, https://doi.org/10.1136/ijgc-2020-002071 Mar. (PMID: 33649002).

[13] P. Modaffari, R. Ponzone, A. Ferrari, I. Cipullo, V. Liberale, M. D'Alonzo, F. Maggiorotto, N. Biglia, Concerns and expectations of risk-reducing surgery in women with hereditary breast and ovarian Cancer syndrome, J. Clin. Med. 8 (3) (2019) 313 Mar 5. doi: 10.3390/jcm8030313. PMID: 30841601; PMCID: PMC6463153.

[14] L. Perez, E. Webster, L. Bull, J.T. Brewer, M.D. Ahsan, J. Lin, S.R. Levi, E. Cantillo, E. Chapman-Davis, K. Holcomb, S.M. Rosenberg, M.K. Frey, Patient perspectives on risk-reducing salpingectomy with delayed oophorectomy for ovarian cancer risk-reduction: a systematic review of the literature, Gynecol. Oncol. 173 (2023 Apr 26) 106–113, https://doi.org/10.1016/j.ygyno.2023.04.006 Epub ahead of print. PMID: 37116391.

[15] D.L. Stan, L.T. Shuster, M.J. Wick, C.L. Swanson, S. Pruthi, J.N. Bakkum-Gamez, Challenging and complex decisions in the management of the BRCA mutation carrier,

J. Women's Health (Larchmt) 22 (10) (2013) 825–834, https://doi.org/10.1089/jwh.2013.4407 Oct. (Epub 2013 Aug 29. PMID: 23987739; PMCID: PMC4047843).
[16] L.S. Matan, T. Perri, L. Kogan, B. Brandt, R. Meyer, G. Levin, Ovarian cancer risk management in BRCA-mutation carriers: a comparison of six international and national guidelines, Eur. J. Obstet. Gynecol. Reprod. Biol. 278 (2022) 166–171, https://doi.org/10.1016/j.ejogrb.2022.09.035 Nov. Epub 2022 Sep 29. PMID: 36208522.
[17] L. Knabben, F. Siegenthaler, S. Imboden, M.D. Mueller, Fertility in BRCA mutation carriers: counseling BRCA-mutated patients on reproductive issues, Horm. Mol. Biol. Clin. Invest. 43 (2) (2020) 171–177, https://doi.org/10.1515/hmbci-2020-0005 Oct 6. (PMID: 33027047).
[18] S. Kostov, R. Watrowski, Y. Kornovski, D. Dzhenkov, S. Slavchev, Y. Ivanova, A. Yordanov, Hereditary gynecologic Cancer syndromes - a narrative review, Onco Targets Ther 8 (15) (2022) 381–405 Apr. doi: 10.2147/OTT.S353054. PMID: 35422633; PMCID: PMC9005127.
[19] Practice Committee of Society for assisted reproductive technology; practice Committee of American Society for reproductive medicine. Preimplantation genetic testing: a practice committee opinion, Fertil. Steril. 90 (5 Suppl) (2008) S136–S143, https://doi.org/10.1016/j.fertnstert.2008.08.062 Nov. (PMID: 19007612).
[20] J.L. Chan, L.N.C. Johnson, M.D. Sammel, L. DiGiovanni, C. Voong, S.M. Domchek, C.R. Gracia, Reproductive Decision-Making in Women with BRCA1/2 Mutations, J. Genet. Couns. 26 (3) (2017 Jun) 594–603, https://doi.org/10.1007/s10897-016-0035-x Epub 2016 Oct 28. PMID: 27796678; PMCID: PMC5409889.
[21] A.Z. Steiner, D. Pritchard, F.Z. Stanczyk, J.S. Kesner, J.W. Meadows, A.H. Herring, D.D. Baird, Association between biomarkers of ovarian reserve and infertility among older women of reproductive age, JAMA 318 (14) (2017) 1367–1376 Oct 10. doi: 10.1001/jama.2017.14588. PMID: 29049585; PMCID: PMC5744252.
[22] J. Kim, C. Skrzynia, J.E. Mersereau, A pilot study of BRCA mutation carriers' knowledge about the clinical impact of prophylactic-oophorectomy and views on fertility consultation: a single-center pilot study, J. Genet. Couns. 24 (1) (2015) 149–157, https://doi.org/10.1007/s10897-014-9747-y Feb. Epub 2014 Aug 15. PMID: 25120035.
[23] O. Evans, F. Gaba, R. Manchanda, Population-based genetic testing for Women's cancer prevention, Best Pract. Res. Clin. Obstet. Gynaecol. 65 (2020) 139–153, https://doi.org/10.1016/j.bpobgyn.2020.02.007 May. Epub 2020 Mar 2. PMID: 32245629.
[24] K. Oktay, B.E. Harvey, A.H. Partridge, G.P. Quinn, J. Reinecke, H.S. Taylor, W.H. Wallace, E.T. Wang, A.W. Loren, Fertility preservation in patients with Cancer: ASCO clinical practice guideline update, J. Clin. Oncol. 36 (19) (2018) 1994–2001, https://doi.org/10.1200/JCO.2018.78.1914 Jul 1. Epub 2018 Apr 5. PMID: 29620997.
[25] M. De Rycke, V. Berckmoes, Preimplantation genetic testing for monogenic disorders, Genes (Basel) 11 (8) (2020) 871 Jul 31. doi: 10.3390/genes11080871. PMID: 32752000; PMCID: PMC7463885.
[26] F. Gaba, S. Goyal, D. Marks, D. Chandrasekaran, O. Evans, S. Robbani, C. Tyson, R. Legood, E. Saridogan, W.G. McCluggage, H. Hanson, N. Singh, D.G. Evans, U. Menon, R. Manchanda, PROTECTOR team., Surgical decision making in premenopausal *BRCA* carriers considering risk-reducing early salpingectomy or salpingo-oophorectomy: a qualitative study, J. Med. Genet. 59 (2) (2022) 122–132, https://doi.org/10.1136/jmedgenet-2020-107501 Feb. (Epub 2021 Feb 10. PMID: 33568437; PMCID: PMC8788252).
[27] F.A. Peccatori, G. Mangili, A. Bergamini, F. Filippi, F. Martinelli, F. Ferrari, S. Noli, E. Rabaiotti, M. Candiani, E. Somigliana, Fertility preservation in women harboring deleterious BRCA mutations: ready for prime time? Hum. Reprod. 33 (2) (2018) 181–187, https://doi.org/10.1093/humrep/dex356 Feb 1. (PMID: 29207007).
[28] B. Buonomo, C. Massarotti, M. Dellino, P. Anserini, A. Ferrari, M. Campanella, M. Magnotti, C. De Stefano, F.A. Peccatori, M. Lambertini, Reproductive issues in carriers of germline pathogenic variants in the BRCA1/2 genes: an expert meeting, BMC Med. 19 (1) (2021) 205 Sep 10. doi: 10.1186/s12916-021-02081-7. PMID: 34503502; PMCID: PMC8431919.
[29] M. Lambertini, O. Goldrat, A. Toss, H.A. Azim Jr., F.A. Peccatori, M. Ignatiadis, L. Del Mastro, I. Demeestere, Fertility and pregnancy issues in BRCA-mutated breast cancer patients, Cancer Treat. Rev. 59 (2017) 61–70, https://doi.org/10.1016/j.ctrv.2017.07.001 Sep. Epub 2017 Jul 14. PMID: 28750297.
[30] A. La Marca, E. Mastellari, Fertility preservation for genetic diseases leading to premature ovarian insufficiency (POI), J. Assist. Reprod. Genet. 38 (4) (2021 Apr) 759–777, https://doi.org/10.1007/s10815-021-02067-7 Epub 2021 Jan 25. PMID: 33495935; PMCID: PMC8079553.
[31] C E DK, C VTT, J C EM, G W M LE, Irene H, Mariette G, J T VGR, Willem V, D LK, J M BF, M E BA, The impact of BRCA1- and BRCA2 mutations on ovarian reserve status, Reprod. Sci. 30 (1) (2023) 270–282, https://doi.org/10.1007/s43032-022-00997-w Jan. (Epub 2022 Jun 15. PMID: 35705781; PMCID: PMC9810575).
[32] J.M. Haddad, K. Robison, L. Beffa, J. Laprise, J. ScaliaWilbur, C.A. Raker, M.A. Clark, E. Hofstatter, D. Dalela, A. Brown, L. Bradford, M. Toland, A. Stuckey, Family planning in carriers of BRCA1 and BRCA2 pathogenic variants, J. Genet. Couns. 30 (6) (2021) 1570–1581, https://doi.org/10.1002/jgc4.1423 Dec. Epub 2021 Apr 27. PMID: 33904624.
[33] U. Menon, et al., Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer, Hum. Reprod. 22 (6) (2007) 1573–1577.
[34] Gwendolyn P. Quinn, et al., Conflict between values and technology: perceptions of preimplantation genetic diagnosis among women at increased risk for hereditary breast and ovarian cancer, Fam. Cancer 8 (2009) 441-449.