Fertility preservation in patients with BRCA mutations or Lynch syndrome

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ABSTRACT

Guidelines and expert consensus are lacking on fertility preservation in BRCA mutation carriers and in patients with Lynch syndrome. The safety of fertility preservation in this setting is still a topic of debate and multiple factors need to be carefully considered. The aim of this review was to analyze the reproductive potential of women harboring a genetic mutation affecting the DNA repair system and explore the efficacy and safety of existing fertility preservation strategies in these patients.

INTRODUCTION

Hereditary breast and ovarian cancer syndrome, and Lynch syndrome (hereditary non-polyposis colorectal cancer), increase gynecological cancer risks.[1] Both are inherited as autosomal dominant disorders. In particular, hereditary breast and ovarian cancer syndrome is characterized by pathogenic variants in the BRCA1 and 2 genes,[2 3] but other genes involved in the DNA repair process[4 5] might also be involved as damage of these genes increases the risk of breast and ovarian tumors but also of pancreatic and prostate cancer.[4 5] Lynch syndrome is associated with pathogenic variants in a mismatch repair gene family[6] and is associated with an increased risk of colorectal cancer, as well as endometrial, breast, and ovarian cancer.[7 8] Primary and secondary prevention in women carrying these mutations is focused on early cancer detection and/or on prophylactic procedures.

As screening remains of limited value, at least in ovarian cancer, women may choose surgical options, such as risk reducing bilateral salpingo-oophorectomy, bilateral salpingectomy, or hysterectomy to reduce the risk of cancer.[9] Since hereditary cancers are associated with a relatively young onset, risk reducing surgery is generally recommended between the ages of 35–45, or when childbearing is completed[9]; however, these procedures lead to premature menopause and infertility.

In this review, we focus on fertility issues in women harboring a genetic mutation of DNA repair genes, in particular BRCA1 or BRCA2, or with Lynch syndrome.

FERTILITY PRESERVATION IN BRCA 1/2 MUTATION CARRIERS

We performed a literature review to summarize data on the assessment of fertility potential and response to in vitro fertilization techniques on BRCA mutation carriers. We searched Pubmed with the key words 'BRCA and fertility' and found 98 articles between January 2000 and March 2020. We excluded non-English language articles, review articles, surveys, video articles, and non-pertinent articles. We obtained 13 articles reporting data on 3145 patients, of which 2211 were BRCA wild type, 599 BRCA mutated (335 BRCA1, 237 BRCA2, 4 heterozygous BRCA1/2 carriers, 5 mutation of unknown significance, 4 BRCA1–2 mutation, 14 non-specified BRCA mutation types). 245 patients were controls and 90 had an unknown mutation status.

BRCA Status and Fertility Potential

BRCA1 and 2 genes are key members of the kinase ataxia–telangiectasia mutated mediated DNA double strand break repair pathway. The prevalence of BRCA deleterious mutations is approximately 1:300–500 in the general population.[10] Overall, BRCA mutations account for 17–65.5% of breast cancers and 16.2–40% of ovarian cancers. Of specific relevance for the present review is the fact that BRCA related malignancies are characterized by a precocious onset. A 20-year-old patient with a BRCA1 mutation has a 12% and 3.2% risk of developing breast and ovarian cancers, between the ages of 20 and 40 years, respectively. For a similar patient with a BRCA2 mutation, these risks are 7.5% and 0.7%, respectively.[10] Considering the current trend to postpone pregnancy to later in life, especially in Western countries, it is anticipated that an increasing proportion of young women will be diagnosed with cancer before completing childbearing. The most effective measure to reduce the risk of ovarian cancer in BRCA mutated patients is risk reducing salpingo-oophorectomy at age 35–40, but this impairs fertility, inducing a premature menopause.[11]

Moreover, BRCA mutations seem to directly influence the fertility potential of the mutation carrier. In fact, because BRCA genes play critical roles in the repair of double stranded DNA breaks, it is plausible that germline mutations of BRCA genes can lead to accelerated oocyte apoptosis as well as depletion. Titus and colleagues demonstrated in animal models that impairment in DNA double strand break repair caused by BRCA mutation results in accelerated loss of primordial ovarian follicles and ovarian aging.[12] In humans, data on the role of BRCA mutation on fertility potential is less clear. Some authors affirm that mutation carriers, especially BRCA1, have a decreased ovarian reserve, infertility, and primary ovarian insufficiency.[13] Recent evidence suggests that reduction of primordial follicle numbers with increasing age is caused by the rise in DNA double strand breaks; this process is accelerated in BRCA mutation carriers due to deficiency in the ataxia–telangiectasia mutated double strand break repair mechanism.[14]

Alternatively, Pal et al compared parity and fertility in 2254 BRCA carriers and 764 non-carrier controls and found no differences in age at first birth, age at last birth, or mean parity between the groups.[15] Similarly, an epidemiologic study conducted by Smith et al showed that female mutation carriers have more children and shorter birth intervals than matched controls.[16] Therefore, controversial opinions regarding the impact of BRCA mutation on reproductive potential and ovarian reserve remain.

In our search, 11 articles[17–27] considered anti-Mullerian hormone and antral follicular count as indexes of ovarian function in BRCA mutation carriers compared with wild-type controls (Table 1). In fact, anti-Müllerian hormone levels and antral follicular count are considered predictors of ovarian response during in vitro fertilization techniques, with lower levels suggestive of a poor response.[28]

Ovarian Function Assessment

Anti-Müllerian Hormone

The anti-Müllerian hormone is a member of the transforming growth factor β family, which is produced in the granulosa cells of ovarian follicles and can be detected in serum. Several studies have validated anti-Müllerian hormone as a direct biomarker for ovarian aging, which reflects the decline in reproductive capacity.[29 30] In our search, we considered 11 studies[17–27] evaluating anti-Müllerian hormone levels as an index of the ovarian reserve, comparing BRCA carriers with wild-type controls. Four studies concluded that BRCA mutation carriers had lower levels of anti-Müllerian hormone compared with BRCA wild-type patients[17 20 22 23] while five studies had the opposite results, reporting BRCA patients who had higher anti-Müllerian hormone levels compared with BRCA wild-type patients.[18 21 24 26 27] More recently, Oktay et al did not find any differences in anti-Müllerian hormone levels among BRCA mutated compared with BRCA wild-type patients.[19] Therefore, data are still controversial and do not provide reliable information for clinical practice; furthermore, interpretation of study results is complicated due to several confounding factors, such as small and various study populations, different ages and ethnicities, body mass index, use of hormonal contraceptives, and inclusion of patients with breast cancer. Interestingly, Giordano et al found a significant association between low anti-Müllerian hormone concentrations and age in BRCA mutation carriers: women with a BRCA1 mutation over 35 had a 10 times higher risk of low anti-Müllerian hormone (<0.5 ng/mL) than younger women less than 35 years old.[31]

In conclusion, data are controversial and do not provide reliable information in clinical practice; furthermore, interpretation of studies results is complicated by confounding factors, such as small and various study populations, different ages and ethnicities, body mass index, use of hormonal contraceptives, and inclusion of patients with breast cancer

Table 1 Ovarian function and fertility assessment

Fertility assessment				Median age (years)					Sample					Cancer			Fertility assessment: AMH levels					Antral follicular count				
Article	Year	Study type	Patients included	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	Breast	Other	No cancer	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other
Porcu et al[17]	2020	Prospective	227	32.2	31.5	33.2	32.5	32.4	22	11	11	24	181	46	0	181 controls	2.8	1.2	4.4	4.5	3.8	11.65	11.8	11.5	14.2	12.48
Ponce et al	2020	Case control	135	32.35	32.6	32.1	32.7	/	69	32	37	66	0	0	0	0	2.77	3	2.54	2.27	/	/	/	/	/	/
Oktay et al	2020	Longitudinal cohort	108	33.7	/	/	36.1	/	14	0	0	59	35 not tested	108	0	0	2.5	0	0	2.6	3.4	/	/	/	/	/
Son et al	2019	Retrospective	316	34	/	/	34	/	52	27	25	264	0	316	0	0	2.6	2.56	2.64	3.85	/	/	/	/	/	/
Lambertini et al	2019	Prospective	148	34	/	/	36	/	35	22	13	113	0	148	0	0	1.94	1.58	2.78	1.66	/	/	/	/	/	/
Grynberg et al	2019	Retrospective	329	31.7	31.8	31.9	32.3	/	52	36	16	277	0	329	0	0	3.6	3.7	3.2	4.1	/	20.5	21.3	18.4	21.7	/
Lambertini et al	2018	Retrospective	156	31	/	/	31	/	29	19	10	72	55 unknown	156	0	0	1.8	1.8	1.5	2.6	/	/	/	/	/	/
Gunnala et al	2018	Retrospective cohort study	795	32.4	/	/	35.5	/	57	31	18	738	0	91	0	619	2.8	2.4	3.6	2.4	/	15.5	15.5	15.7	12.6	/
Lin et al	2017	Comparative laboratory study	30	36.5	/	/	33	/	18	13	5	12	0	0	0	0	/	/	/	/	/	11.2±6.7 primordial follicles/mm^3	0	0	44.18±6.1	No differences between BRCA1 and 2
Johnson et al	2017	Prospective	195	31.15	31.4	30.9	34.3	30.9	105	55	50	26	64	0	0	0	2.99	3.26	2.72	2.13	3.20	/	/	/	/	/
Michaelson-Cohen et al	2014	Prospective	365	33.2	/	/	/	/	41	26	12	324	0	0	0	0	2.71	2.48	1,71	2.02	/	/	/	/	/	/

AMH, anti-Müllerian hormone; WT, wild-type.

Antral Follicular Count

Antral follicle count is the count of resting follicles found on both ovaries at the beginning of the proliferative phase of the menstrual cycle using transvaginal ultrasound, which is a marker of ovarian reserve and of the primordial follicle number, even after adjustment for chronological age.[32]

A correlation between the presence of a BRCA mutation and higher follicular count has been proposed, but data are few and controversial. We identified four studies[17 22 24 25] which investigated this association: Gunnala et al[24] found statistically higher antral follicular counts in BRCA mutated women in comparison with the wild-type population (p<0.001) but no significant differences between BRCA1 and BRCA2 mutation carriers (p=0.861). Nonetheless, other experiences did not confirm these findings, and population bias and small cohort sizes made results partially inconsistent. Overall, it might be affirmed that no compelling evidence seems to support that the rate of antral follicle counts and ovarian response are affected in BRCA mutation carriers.

BRCA MUTATED PATIENTS AND ASSISTED REPRODUCTIVE TREATMENTS

Evidence in the literature suggests that fertility treatments are not associated with an increased risk of gynecologic or breast cancers, even in BRCA mutation carriers.[33] Gronwald et al performed a matched case-control study on 941 pairs of BRCA1 or BRCA2 mutation carriers with and without a diagnosis of ovarian cancer, adjusted for gene mutation (BRCA1 or BRCA2), age, parity, oral contraceptive use, and prior diagnosis of breast cancer. The authors found no relationship between in vitro fertilization and ovarian cancer risk (odds ratio=0.33, 95% confidence interval 0.04 to 3.30; p=0.35). Although limited by the small number of women who used fertility medications (n=63), no significant relationship between the use of specific drugs and ovarian cancer occurrence was noted.[34] These data suggest that there is no contraindication to the use of fertility medications or in vitro fertilization in BRCA mutated patients. In the following two sections, we will focus on the two most common techniques of fertility preservation: oocyte and/or embryo cryopreservation and ovarian tissue cryopreservation.

Oocyte and/or Embryo Cryopreservation

The cryopreservation of oocytes is the first recommended fertility preservation technique for cancer patients, which is only indicated for patient either able to postpone cancer therapy for 2–3 weeks and/or without contraindication for ovarian stimulation. It is a valid option for postpubertal women without male partners or those who do not accept sperm donation or have moral objections to embryo cryopreservation. For obvious reasons, oocyte freezing is unsuitable for prepubertal girls because it requires ovarian stimulation.[35]

In our review, we identified six studies[17 22–24 36 37] which included 1848 patients: 265 with BRCA mutation (160 BRCA1 mutated, 95 BRCA2 mutated, 9 with unknown mutation, 1 with BRCA 1–2 mutation), 1528 patients were BRCA wild-type, and 55 patients had unknown mutational status (Table 2). Some studies reported a lower response to stimulation in BRCA mutated patients[38] and the results were unconfirmed in other studies.[36] In the recent past, a French study compared in vitro maturation rates of recovered immature oocytes in 57 BRCA mutated versus 277 negative controls without

Table 2 Ovarian function and fertility preservation

Fertility preservation				Median age (years)					Sample					Cancer			Total dose of gonadotropins					No of oocytes retrieved					No of oocytes cryopreserved				
Article	Year	Type of study	No of patients	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	Breast cancer	Other cancer	No cancer	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other	BRCA mutated	BRCA 1	BRCA 2	BRCA WT	Other
Porcu et al[17]	2020	Prospective study	227	32.3	31.5	33.2	32.5	32.4	22	11	11	24	181	46	0	181	2126	2206	2047.5	2106.3	1597	8.35	6.7	10	9.1	8.8	5.35	3.1	7.6	7.2	7.3
Grynberg et al	2019	Retrospective study	329	31.7	/	/	32.3	/	52	36	16	277	0	329	0	0	/	/	/	/	/	8.9	9.1	8.1	9.9	/	5.1	4.9	5.4	6.1	/
Gunnala et al	2019	Retrospective study	795	32.4	/	/	35.5	/	57	31	18	738	8*	91	0	619	3166.4	2958.8	3283.3	3329	/	16.6	15.5	17.1	13.5	/	14.0	13.5	14.2	10.4	/
Lambertini et al	2018	Retrospective study	156	31	/	/	31	/	29	19	10	72	55*	156	0	0	2775	2775	2775	2025	/	6.5	7	6	9	/	3.5	5	3	6	/
Derks-Smeets et al	2017	Retrospective study	217	31.4	/	/	32.1	/	43	20	23	174	0	0	0	0	1987.5	1950	2137.5	1950	/	7	6.5	7.5	8.0	/	/	/	/	/	/
Shapira et al	2015	Retrospective study	124	31.92	/	/	32.09	/	62	43	17	62	1*	42	0	82	2482	/	/	2658	/	13.75	/	/	14.75	/	/	/	/	/	/

*unknown.
WT, wild-type.

detecting significant differences.[22] Recently, Porcu and colleagues performed a prospective study including 67 women affected by breast cancer who had undergone fertility preservation treatment compared with 181 healthy controls. They found that patients in the BRCA positive cohort, especially BRCA1 positive patients, needed a higher dose of gonadotropins, a longer duration of stimulation, and a statistically significant lower number of oocytes cryopreserved.[17]

In conclusion, there is growing evidence indicating that BRCA mutations may be associated with decreased ovarian reserve and premature menopause, especially for BRCA1 mutation patients. Therefore, some authors suggest systematic fertility preservation in this population. The cryopreservation of oocytes or embryos can be discussed, emphasizing that the chances of success decrease with increasing age. Hence if these strategies are considered, this should take place at an earlier age, for example, before age 30 years and ideally before cancer diagnosis.

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation maintains both fertility and endocrine ovarian function but it is still considered an experimental technique. This method does not require ovarian stimulation and offers the opportunity of a spontaneous pregnancy. Ovarian tissue cryopreservation might be proposed to selected patients, including some cancer patients scheduled for highly gonadotoxic treatment, but in particular if treatment initiation cannot be delayed, in the case of prior exposure to chemotherapy, when ovarian stimulation is a contraindication, or to prepubertal women.[10] Ovarian tissue is surgically retrieved and cryopreserved. After being thawed, ovarian tissue is grafted back to the patient, on either the orthotopic (into the pelvic cavity) or heterotopic site (subcutaneous regions such as the forearm or abdominal wall).

In BRCA mutated women, younger than the recommended age for prophylactic bilateral salpingo-oophorectomy, the procedure might be feasible. Ovarian tissue can be transplanted into the remaining ovaries so that the gonads can be removed after completion of reproductive plans. Another strategy may be subcutaneous transplantation of ovarian tissue for better monitoring.[23] In Lambertini et al's study[23] 72 patients underwent ovarian tissue cryopreservation. Patients in the BRCA positive cohort tended to have a numerically lower number of oocytes per fragment (0.08 vs 0.14; p=0.19) than those in the BRCA negative cohort (0.14 number of oocytes per fragment). Currently, two cases of pregnancy obtained by ovarian tissue cryopreservation in BRCA mutated women have been published. In both cases, BRCA2 mutation carriers, previously treated for breast cancer, became pregnant after ovarian tissue transplantation 55 and 36 months following completion of chemotherapy. This suggests that cryopreservation might be a safe and effective option for BRCA mutated patients desiring fertility after cancer treatment.

LYNCH SYNDROME

Evidence regarding fertility issues and Lynch syndrome are limited, and even more so when searching for other genes involved in the DNA repair pathway. A systematic review was not possible due to the paucity and heterogeneity of the data. Nonetheless, we want to highlight some major issues, as this condition, although rare, has been diagnosed more frequently in recent years due to the greater attention and knowledge of hereditary cancer syndromes. Lynch syndrome (previously referred to as hereditary non-polyposis colorectal cancer) is an autosomal dominantly inherited cancer syndrome characterized by the development of colorectal, endometrial, and ovarian cancers and various other neoplasia frequently diagnosed at an early age. It is caused by pathogenic variants of the DNA mismatch repair system genes MLH1, MSH2, MSH6, and PMS2, which prevent the correction of acquired errors during DNA synthesis.[39] Gynecological cancers are often the sentinel Lynch syndrome event in women and have an excellent prognosis.[40] The risk of developing endometrial cancer is very high and equals or exceeds the risk of colorectal cancer among women with Lynch syndrome.[41] The cumulative incidence of endometrial cancer for pathological MLH1, MSH2, MSH6, and PMS2 is 42.7%, 56.7%, 46.2%, and 26.4% at the age of 75 years, respectively.[8] Typically, women affected by Lynch syndrome are younger than unaffected women: in fact, the average age at endometrial cancer diagnosis in women with Lynch syndrome was reported to be 47–49 years (range 26–87)[7–42] which is more than 10 years younger than the general population affected by endometrial cancer.[43] Ovarian cancer is considered the third most common cancer among women with Lynch syndrome[44]; risk estimates of developing ovarian cancer in patients affected by Lynch syndrome are approximately 8–10%,[6] compared with a 1.4% risk in the general population.[45] The average age of Lynch syndrome patients developing ovarian cancer is between 40 and 47 years of age which is lower than the general population affected, but higher than BRCA1 mutation carriers who develop ovarian neoplasia.

In recent years, clinical practice and guidelines for gynecological surveillance and prophylactic surgery for female Lynch syndrome variants have been evolving. According to the National Comprehensive Cancer Network guidelines,[9] total hysterectomy and bilateral salpingo-oophorectomy are options in women with Lynch syndrome who have completed childbearing, in order to reduce the risk of both endometrial cancer and ovarian cancer. The timing of risk reducing surgery may be individualized based on family history and comorbidities[9] and is not standardized, as it is in BRCA mutation carriers. Noteworthy, women diagnosed with Lynch syndrome face both a higher risk of developing cancers and the need to undergo risk preventive procedures, which may adversely impact their fertility potential. In contrast with BRCA mutation carriers, it is unclear whether or not Lynch syndrome itself is associated with impairment of fertility potential. Although mismatch repair proteins are essential in DNA replication, no evidence in the current literature suggests that Lynch syndrome directly affects fertility.[46] In the only study addressing this issue, Stupart et al[47] proposed a model in which they found a decrease in lifetime fertility in patients with Lynch syndrome and affected by an early diagnosis of colorectal cancer, compared with those who developed colorectal cancer later in life. For example, women diagnosed with colorectal cancer between the ages of 20 and 24 gave birth to a mean of 1.2 children in their lifetime compared with women diagnosed with colorectal cancer after age 50 years who gave birth to a mean of 2.8 children in their lifetime. The reasons for reduced fertility after colorectal cancer in these patient groups were not investigated in the study, but cancer related mortality and morbidity, effects of surgery, chemotherapy and radiotherapy, and personal choice can all be expected to play a role. However, it should be emphasized that this is the only experience suggesting this reduction and no biological explanations have been anticipated.

When considering Lynch syndrome and endometrial cancer risk, it should be considered that because endometrial cancer is detected at earlier ages, it is common that some patients might be diagnosed when still premenopausal and with an unresolved fertility desire. Therefore, the issue of conservative treatment becomes particularly challenging. In the overall population, accumulating evidence highlights that fertility sparing options might be offered to young women diagnosed with endometrial hyperplasia or cancers limited to the endometrium. Conservative treatment in most cases consists of progestin administered orally or via a levonorgestrel coated intrauterine device.[48 49] Moving to atypical hyperplasia or limited endometrial cancer, fertility preservation is more complicated because endometrial lesions are caused by genetic mutations and the efficacy of fertility sparing hormonal treatment remains debatable. In fact, it should be noted that the molecular mechanisms causing disease in patients with Lynch syndrome differ from those occurring in sporadic cases. Therefore, progestin therapy, which is more commonly used in the latter group, may be ineffective[48] in patients harboring a defect in mismatch repair genes.[50]

Accordingly, in the guidelines and expert consensuses discussing fertility sparing treatment for atypical hyperplasia and endometrial cancer in Lynch syndrome patients, this issue is still debated and the safety of fertility sparing treatment in Lynch syndrome patients remains unclear, if not unproven. Interestingly, in a recent survey among gynecological oncologists on this issue, the majority of clinicians did not support the choice of conservative management and fertility preservation in endometrial cancer with Lynch syndrome.[49] The authors concluded that patients have to be counseled about the risk of developing disease recurrence/persistence. Additionally, as they are at a significantly higher risk of developing ovarian cancer, the importance of performing risk reducing surgery, after patients have completed childbearing, should be emphasized.

Additional Cancer Related Genes and Impact on Fertility

With regard to other genes involved in DNA repair, several have been investigated and are related to gynecological cancer occurrence. In particular, women carrying a germline pathogenic variant in BRIP1 have an 8–11-fold increased relative risk of developing ovarian cancer, without a significantly increased risk for breast cancer. Also, pathogenic variants in RAD51C and RAD51D are associated with an increased risk for ovarian cancer without a significantly increased risk for breast cancer. In contrast, pathogenic variants in TP53, CDH1, CHEK2, and ataxia–telangiectasia mutated are associated with an increased risk of breast cancer without a significantly increased risk of ovarian cancer.[1] As for BRCA mutation carriers, these hereditary cancers are associated with a relatively younger age of onset, and risk reducing surgeries are generally considered as the best option to prevent cancer development and are recommended between the ages of 35 and 45, or when childbearing is complete. No data about fertility function are available in these women, probably due to the low incidence of these mutations in the general population, with few available reports and, consequently, limited guidelines. Accordingly, no data about assisted reproductive technology procedures or oocyte conservation have been presented.

ETHICAL ISSUES

Gamete or gonad storage for long periods generates ethical and moral questions deserving of attention, reflection, and discussion before a fertility preservation protocol is considered. One reason for such discussion is the existence of uncertainties curtailing the processes that involve routine and experimental strategies, as well as the future use of the preserved tissues and cells if the biological owner dies. Fertility preservation preceding antineoplastic treatment lays between medical indication, based on the intention of prevention, humanization, and a social statement based on the biopsychosocial impact of procreating. In the case of cancer patients with a potential risk of fertility loss, the main ethical issue is to furnish the best information about the potential risks and the currently available techniques for the preservation of their gametes. This will allow well informed patients and their families to make the right decisions with the necessary clarity, based on personal interest concerning the possibility of future fertility.

CONCLUSIONS

Genetic testing rates for BRCA mutations or Lynch syndrome have progressively increased during the past decades resulting in a growing population of young and healthy patients with genetic alterations. For these young women, fertility is an issue as their fertile window has reduced due to prophylactic surgery and cancer treatments, and likely a reduced fertility potential. Data on fertility preservation techniques are still scant in this populations and the aim of this review was to summarize the most up to date evidence on this emerging topic. Remarkably, there is emerging but not completely accepted evidence that BRCA mutations may cause a decrease in ovarian reserve, with premature menopause. Therefore, some have proposed fertility preservation techniques in this population, with some concern about a possible increased risk of cancer. Preventive intervention is mandatory; nonetheless, identification of these women, at a young age, would allow fertility counseling and a tailored approach. In particular, these women should be advised against delaying childbearing.

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