Reproductive Health in Xeroderma Pigmentosum

Features of Premature Aging

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OBJECTIVE: To assess the age at menarche and menopause of women with xeroderma pigmentosum, a DNA repair disease with premature aging, in a longitudinal natural history study.

METHODS: We conducted a natural history study that reviewed medical records for gynecologic and reproductive health of all female patients with xeroderma pigmentosum aged older than 9 years examined at the National Institutes of Health (NIH). We performed gynecologic and laboratory examinations on a subset of the patients. Women in a second subset, who could not be examined, were interviewed using a questionnaire. Women who were deceased or lost to follow-up formed a third subset.

RESULTS: Sixty females with xeroderma pigmentosum aged older than 9 years (median 29 years, range 10–61 years) were evaluated at the NIH from 1971 to 2018. Of these 60, 31 had history, questionnaire, record review, and gynecologic evaluation; 14 had record review and questionnaire interview by telephone; and 15 had only NIH record review. Menarche in females with xeroderma pigmentosum occurred at a median age of 12.0 years (range 9–17 years), which was comparable with the U.S. general population. Among the 18 patients with menopause, the median age at menopause of 29.5 years (range 18–49.5 years) was more than 20 years younger than in the U.S. general population (52.9 years). Premature menopause (before age 40 years) occurred in 14 of the 45 (31%) women aged 18 years or older, and primary ovarian insufficiency was documented in nine of them. There were 32 live births among 21 of the women, five of whom subsequently developed premature menopause.

CONCLUSION: Females with xeroderma pigmentosum in our study had a normal age at menarche and were fertile but had increased incidence of premature menopause. Premature menopause, a symptom of premature aging, should be considered for gynecologic and reproductive health as well as implicating DNA repair in maintaining normal ovarian function.

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Divya Angra reports receiving money paid directly to her from NCI. John J. DiGiovanna reports that he is an employee of the National Institutes of Health (Federal Government) and they pay salary and travel costs to meetings. He is an independent contractor performing dermatology services for Shady Grove Dermatology. Prior to November 2018 he ran a part-time practice of dermatology, which was transferred to Shady Grove Dermatology. The other authors did not report any potential conflicts of interest.

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Xeroderma pigmentosum is a rare (1 per million people in the United States and Europe)[1] autosomal recessive disorder caused by mutations in any of seven genes (complementation groups XP-A to XP-G) in the DNA nucleotide excision repair transcription

pathway or in *polymerase eta* (xeroderma pigmentosum variant), a bypass polymerase.[2] Xeroderma pigmentosum is seen in higher frequencies in several parts of the world, such as 1 per 22,000 people in Japan[3] and 1 per 10,000 people in northern Africa.[4] Clinical manifestations of xeroderma pigmentosum include acute burning of the skin on minimal sun exposure, features of premature aging including freckle-like (lentiginous) pigmentation on sun-exposed skin before 2 years of age, and a 10,000-fold increased risk of skin cancer before age 20 years.[2] Patients with xeroderma pigmentosum have early onset of ocular abnormalities, including ocular cancer.[5] Approximately 25% of patients with xeroderma pigmentosum develop features of premature aging of the nervous system, with neurologic degeneration characterized by progressive ataxia, loss of reflexes, cognitive decline, and accelerated age-related sensorineural hearing loss often requiring hearing aids.[6–8]

We have been performing a longitudinal natural history study of patients with xeroderma pigmentosum at the National Institutes of Health (NIH) for more than 40 years.[6] Until recently, most patients with xeroderma pigmentosum died from cancer or xeroderma pigmentosum neurologic disease in the second or third decades of life.[6] However, with better cancer treatments, improved methods of ultraviolet protection, and better management of neurologic complications, patients with xeroderma pigmentosum are living longer.[7] Our goal was to assess the reproductive health of women in this study. We assessed their ages of menarche and menopause as well as their pregnancies and number of children.

METHODS

The patients in this natural history study were evaluated under an institutional review board–approved protocol (99C-0099) at the National Cancer Institute of the NIH.[5,6,8–10] Written informed consent was obtained from all participants or from the parents of minor patients. Patients were referred to the NIH for evaluation and treated by outside health care providers. All females with a molecular or clinical diagnosis of xeroderma pigmentosum examined at NIH from 1971 to 2018 were ascertained using the NIH medical records system. Females who were older than 9 years of age at the time of last observation were included in the present study. All outpatient gynecologic evaluations were performed by one of the authors (M.M.) and included review of obstetric–gynecologic history; a questionnaire including information about menarche, childbearing, and menopause; physical examination; and laboratory testing. Pelvic and thyroid ultrasound scans and dual energy X-ray absorptiometry scans for bone density were performed on selected patients. Laboratory blood tests varied among the patients and included complete blood count, follicle-stimulating hormone (FSH), serum estradiol, antimüllerian hormone, intact parathyroid hormone, osteocalcin, bone-specific alkaline phosphatase, thyroid stimulating hormone, free thyroxine, thyroglobulin, antithyroglobulin, serum human chorionic gonadotropin, luteinizing hormone, serum progesterone, prolactin, sex hormone binding globulin, total testosterone, free testosterone, 25 hydroxy-vitamin D, 1,25 dihydroxy-vitamin D, vitamin B12, folic acid, adrenal 21-hydroxylase antibody, immunoglobulin levels, hemoglobin A1C, and fragile X chromosome evaluation (expansion of CGG DNA triplet repeat within the *FMR1* gene). Where possible, we looked for evidence of primary ovarian insufficiency, including patient-reported symptoms, laboratory findings, and vaginal atrophy on examination. In addition, a subset of patients who had been seen at the NIH previously but had not had gynecologic examinations was interviewed by telephone using a questionnaire to obtain data on gynecologic and reproductive health issues. All data were recorded on Excel spreadsheets and reviewed by two authors (M.M. and D.T.) for accuracy. Medical records from deceased patients and patients lost to follow-up were analyzed for gynecology reports, history of premature menopause, and laboratory test results. These records consisted of archived electronic NIH medical records and medical records stored offsite that had been requested for review. Ages at menarche and menopause between the patients with xeroderma pigmentosum and U.S. Caucasian females[11,12] were compared using χ^2 or Fisher exact tests. Results with $P<0.05$ were regarded as significant.

RESULTS

From 1971 to 2018, 85 female patients with xeroderma pigmentosum were seen at the NIH as part of a DNA repair disease longitudinal natural history protocol. Of these, six patients did not meet the age requirement of at least 9 years of age at the time of the visit, 10 patients were found to have the overlap syndromes of either xeroderma pigmentosum–trichothiodystrophy or xeroderma pigmentosum–Cockayne syndrome[2] and were not included, and there was no gynecologic information for nine women. A total of 60 patients met the inclusion criteria (Table 1). Of these 60, 31 had obstetric–gynecologic history, questionnaire, record review, and gynecologic evaluation during their NIH visit; 14 had record review and questionnaire interview by telephone; and 15 had only NIH record review (these were primarily deceased patients).

Table 1. Females With Xeroderma Pigmentosum Aged Older Than 9 Years, 1971–2018, in National Institutes of Health Cohort

	Complementation Group*							
	Total	XP-A	XP-C	XP-D	XP-E	XP-G	XP Variant	Unknown
Age at last observation (y)	n=60	n=7	n=27	n=13	n=2	n=1	n=4	n=6
Median	29	22	31	28	55.5	28	49	33
Range	10–61	12–44	10–61	14–52	52–59		39–60	12–57
Age at death (y)	n=12	n=2	n=5	n=3	n=0	n=0	n=0	n=2
Median	34		35	36				
Range	24–49	24–44	28–49	28–45				24–28
Age at menarche known (y)	n=56	n=7	n=24	n=12	n=2	n=1	n=4	n=6
Median	12	12	12	12	14.5	11	12.3	11.5
Range	9–17	9–13	9–17	10–16	14–15		12–13	11–13
Age at nonsurgical menopause known (y)	n=18	n=0	n=15	n=0	n=1	n=0	n=1	n=1
Median	29.5		28		49.5		47	38.5
Range	18–49.5		18–42					
Primary ovarian insufficiency documented	n=9	n=0	n=9	n=0	n=0	n=0	n=0	n=0

* Complementation groups correspond to different genetic mutations.[2]

The 60 patients with xeroderma pigmentosum included in the study ranged in age from 10 to 61 years, with a median age of 29 years (Table 1 and Fig. 1 A and B). The race or ethnicity was 80% Caucasian patients, 13% African American, 3% Hispanic, and 2% each Indian-American and Native American. The largest group of patients was in the XP-C complementation group (n=27, 45%), followed by XP-D (n=13, 22%); there was a smaller number of patients with XP-A, XP-E, XP-G, XP-variant or with an unknown complementation type (Table 1). This distribution of patients with xeroderma pigmentosum is similar to that in Europe.[13] Menarche occurred at a median age of 12.0 years (range 9–17 years), which is similar to the U.S. general population of 12.6 years[11] (Table 1 and Fig. 2).

There were 48 women aged 18–61 years. Three of them had surgically induced menopause. Of the others, nonsurgical menopause was reported in 18 of 45 (40%), with age at menopause ranging from 18 to 49.5 years (Table 1 and Fig. 1A). Premature menopause (before age 40 years) occurred in 14 of 45 (31%) of the women aged 18 years or older, representing 14 of 18 (78%) of the menopausal women (Fig. 1A). Among 33 women in the cohort aged 18–39 years at last observation, 10 (30%) had premature menopause. Among the 15 women age 40 years or older at last observation, four (27%) reported premature menopause, four (27%) had menopause at age 40 years or older, three had surgical menopause, two had died,[10] and two did not report menopause (Fig. 1 A and B). Mutations in the *XPC* DNA repair gene were reported for 13 of the 14 women with premature menopause, and one patient had an unknown xeroderma pigmentosum gene mutation. The proportion of women with premature menopause in this sample was significantly different compared with the general population[13] ($P<.001$). In addition, among the 18 women with menopause, the median age at nonsurgical menopause (29.5 years) was more than 20 years younger than the median age in the U.S. general population of Caucasian women, which is 52.9 years[12] (Fig. 3).

Primary ovarian insufficiency was documented in 9 of the 18 menopausal women on the basis of amenorrhea and two or more blood tests at least 4 months apart showing elevation of FSH (greater than 40 milli-international units/mL). In addition, several of the women also had reduced estradiol levels (less than 20 pg/mL) or undetectable levels of antimüllerian hormone or both (Appendix 1, available online at http://links.lww.com/AOG/B547).

There were 45 pregnancies among 21 of the women (range 1–4 pregnancies per woman). There were 32 live births, 10 spontaneous abortions, and three elective terminations. The women had 26 vaginal births and six cesarean deliveries. At the time of last live birth, the mothers with xeroderma pigmentosum ranged in age from 19–34 years. Premature menopause subsequently developed in five of these mothers with xeroderma pigmentosum at ages 26, 26, 29, 37, and 38.5 years. As expected for this recessive disorder, none of the children of the mothers with xeroderma pigmentosum had clinical features of xeroderma pigmentosum. The children would be obligate heterozygotes.

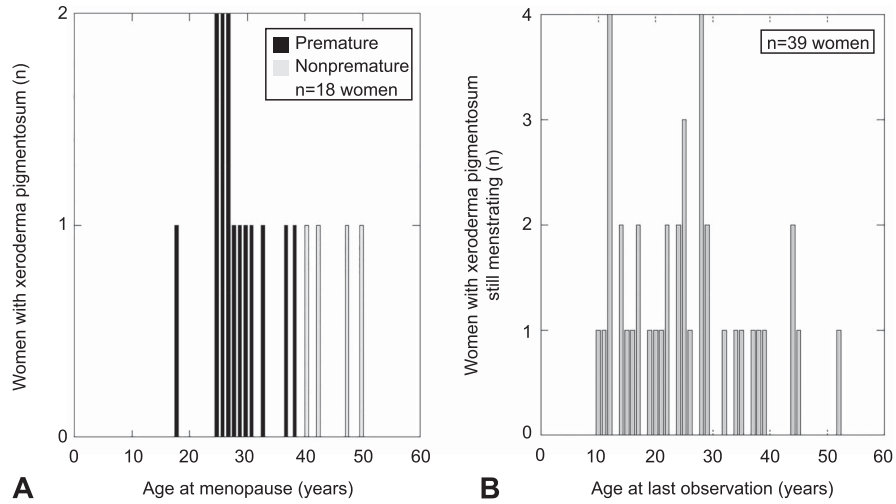

Fig. 1. Age distribution and age of menopause of women with xeroderma pigmentosum. **A**. Eighteen women had menopause, and 14 of them (78%) had premature menopause (before 40 years of age). **B**. Thirty-nine women aged 10–52 years were still menstruating.

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Twelve of the patients have died, with a median age at death of 34 years (range 24–49 years), underscoring the seriousness of the condition (Table 1). Premature menopause was diagnosed in three of the women who died (XP1BE, menopause at 25 years, death from uterine cancer at 49 years[10]; XP26BE, menopause at 27 years, death from cancer invasive to the brain at 33 years[6]; XP24BE, menopause at 27 years, death from glioblastoma at 35 years[10]). Their cancer treatments occurred after the onset of premature menopause and included chemotherapy and radiation. Causes of death for the other nine women were neurologic degeneration (n=3), cancer metastatic to the brain (n=2), pneumonia (n=1), drug overdose (1), and unknown (n=2).[6,10]

DISCUSSION

In this cohort of 60 females with xeroderma pigmentosum, we report the finding of normal age of menarche but premature menopause. Menopause is the permanent cessation of menses due to depletion of ovarian follicles.[14] The mean±SD age at nonsurgical menopause in the U.S. is 50±4 years. Menopause before the age of 40 years is considered to be premature.[14] Primary ovarian insufficiency is defined as a woman younger than age 40 years with amenorrhea or irregular periods for 4 months plus two elevated FSH values in the postmenopausal range (greater than 40 milli-international units/mL) at least 1 month apart. Hypoestrogenism and reduced antimüllerian hormone levels also support the diagnosis. The frequency of primary ovarian insufficiency for women in the general U.S. population is about 1% by the age of 40 years.[14] In our study, 31% (14/45) of the women with xeroderma pigmentosum aged 18–61 years at last observation had nonsurgical menopause before 40 years of age (Figs. 1A and 3). Nine of them

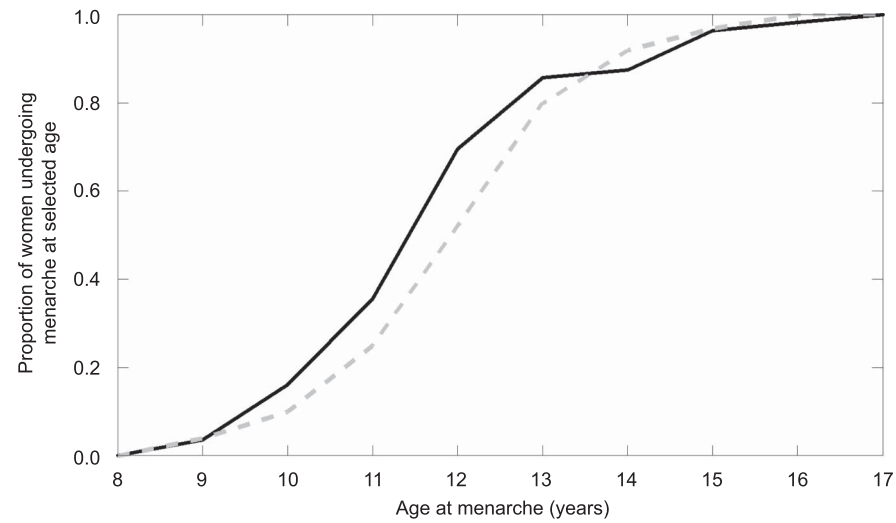

Fig. 2. Age at menarche in 56 women with xeroderma pigmentosum (*solid curve*) vs 1,302 women in the U.S. general population (*dashed curve*). There was a similar median age of 12.0 years in both groups. (U.S. general population data from McDowell MA, Brody DJ, Hughes JP. Has age at menarche changed? Results from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. J Adolesc Health 2007;40:227–31).

Merideth. Premature Menopause in Xeroderma Pigmentosum. Obstet Gynecol 2019.

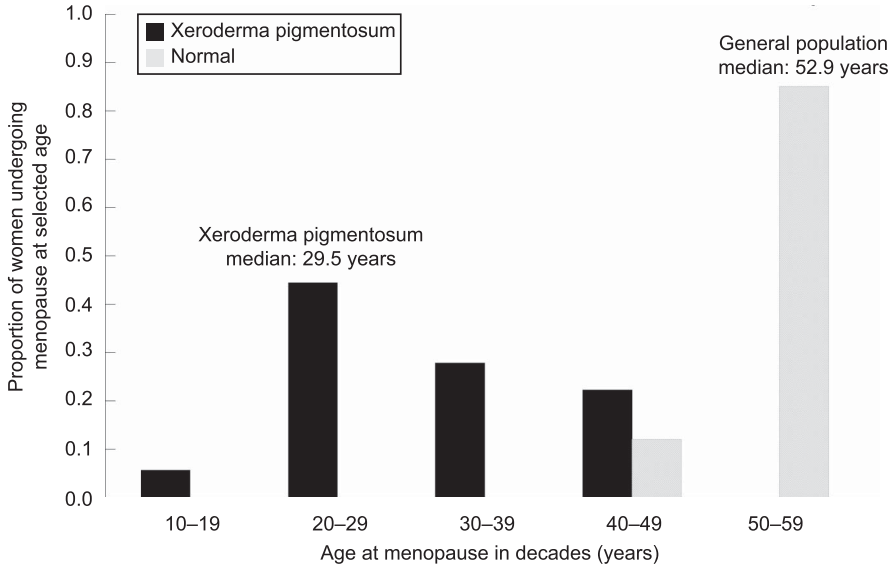

Fig. 3. Age of the proportion of women undergoing menopause in the xeroderma pigmentosum patient group (n=18) vs age of the proportion of women undergoing menopause in the U.S. general population (n=1,533). The women with xeroderma pigmentosum reached menopause about 20 years earlier than the Caucasian women in the control group (median 29.5 years vs 52.9 years). (U.S. general population data from Gold EB, Crawford SL, Avis NE, Crandall CJ, Matthews KA, Waetjen LE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 2013;178:70–83).

Merideth. Premature Menopause in Xeroderma Pigmentosum. Obstet Gynecol 2019.

have been documented as having primary ovarian insufficiency (Table 1 and Appendix 1, http://links.lww.com/AOG/B547). The cause of primary ovarian insufficiency is not determined in about 90% of women in the general population.[14]

Premature menopause has been observed in other DNA repair diseases, including Fanconi anemia, Bloom syndrome, Werner syndrome, and ataxia-telangiectasia,[15] but has not been generally recognized in xeroderma pigmentosum. Despite observing age at menarche similar to that of the general population, the median age at menopause of 29.5 years among the 18 women with xeroderma pigmentosum who reported menopause is more than 20 years younger than the median age in the general population.[11] Most of the patients with premature menopause in our cohort have mutations in the *XPC* gene (complementation group XP-C). However, *XPC* is the most common cause of xeroderma pigmentosum in the United States[6] and it is possible that patients with mutations in other nucleotide excision repair genes may also be affected. Additional data need to be collected on patients with xeroderma pigmentosum with mutations in other nucleotide excision repair genes. This study is limited by its small sample size, variable follow-up, and age at evaluation for menopause or no menopause.

We did not observe other known causes of primary ovarian insufficiency, including fragile X syndrome or other chromosomal abnormalities, thyroid function abnormalities, adrenal abnormalities, hypoparathyroidism, radiation, or chemotherapy[14,16] in our patients. Premature menopause can be caused by an increased loss of follicles, more rapid destruction of follicles, or failure of the follicles to respond to gonadotropins.[14] Our index patient (XP24BE, Appendices 2 and 3, available online at http://links.lww.com/AOG/B547) had primary ovarian insufficiency and mutations in the *XPC* DNA repair gene.[17] At autopsy she was found to have small ovaries with microscopic fibrosis and absent follicles.[10] Normal ovaries are rapidly proliferating and have been reported to have among the highest levels of *XPC* mRNA.[18] This may reflect a greater need for proofreading of newly replicated DNA strands or of repair of endogenous DNA damage or both. Thirteen of the 14 women with premature menopause in our study had mutations in the *XPC* gene (Table 1 and Appendix 1 [Appendix 1, http://links.lww.com/AOG/B547]). These are associated with low levels of *XPC* mRNA and reduced DNA repair.[17] Thus, reduced levels of XPC protein may be another cause of primary ovarian insufficiency.[14] Patients with Fanconi anemia have premature menopause with mutations in the interstrand cross-link repair pathway, and patients with Bloom and Werner syndromes have mutations in RecQ helicase genes, which are important for homologous recombination and nonhomologous end joining.[19] These observations suggest that maintenance of genome stability by multiple DNA repair pathways plays a role in the maintenance of normal ovarian function. The exact mechanism underlying premature menopause in these women with defects in DNA repair is still under debate; however, there is evidence that the ovaries in women with Fanconi anemia may sustain unrepaired double strand breaks that, over time, result in loss of primary follicles.[20] Because developmental

abnormalities such as short stature, dysmorphic features, and limb abnormalities can be seen in some patients with DNA repair disorders, there may be a decreased number of primary ovarian follicles, resulting in exhaustion of viable follicles at an earlier age.[14]

The age when menopause begins may be an indicator of aging and of general health. Later age at menopause has been associated with clinical outcomes such as longer overall survival, greater life expectancy, reduced all-cause mortality, reduced loss of bone density, and reduced fracture risk (see reference 21 and references therein). In our 18 postmenopausal patients with xeroderma pigmentosum, the average age of cessation of menses was 29 years. With better management of skin cancers and good sun protection, these women are living active lives. Knowledge about the increased risk of early menopause for women with xeroderma pigmentosum may affect decisions regarding reproductive choice and timing of childbearing. Young women with xeroderma pigmentosum may benefit from increased surveillance of hormone levels and ultrasound testing in their 20s to help identify diminished ovarian reserve and guide reproductive health recommendations and use of hormone replacement when indicated.[16,22] Specialists in obstetrics and gynecology who provide gynecologic care for women with xeroderma pigmentosum can play an important role in advising about these reproductive health issues and monitoring for adverse effects of premature menopause, such as those on bone, the cardiovascular system, stroke, and malignancy.[21]

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