

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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obgyn@greenjournal.org.

Date: Jun 06, 2019
To: "Kenneth H. Kraemer" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-825

RE: Manuscript Number ONG-19-825

Premature menopause in xeroderma pigmentosum: a newly recognized manifestation of premature aging

Dear Dr. Kraemer:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 27, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Meredith and colleagues describe premature menopause in women with xeroderma pigmentosum. Comments for the authors:

Overall

1. Overall this is an important study of a rare disease that leverages a unique cohort of patients.

Abstract

2. Was menopausal status known on only 18 patients?
3. Were these patients followed longitudinally or was this just a one time evaluation/survey?

Introduction

4. Excellent overview of XP.
5. While the index case is interesting, it is not the typical format for a research paper for the journal. Would consider removing.
6. Claims of primacy (premature menopause not previously reported) generally require justification.

Methods

7. Should clarify a bit the care of patients. These patients were primarily managed at the NIH or these were referrals for opinion and managed by outside providers?
8. Were questions and testing for menopause used throughout the study? Were there standard patient intake forms or questionnaires or was data just abstracted if it happened to be reported?
9. How was age at menarche in the controls determined?

Results

10. One sentence paragraphs (lines 116-117) should be avoided.

Discussion

11. Overall well written but should contain a brief discussion of limitations-incomplete data, menopausal status not recorded, etc.

Reviewer #2: The authors present data on menarche and menopause in women with xeroderma pigmentosum (XP), a rare DNA repair disease. They conclude that women with XP had a normal age of menarche but an increased incidence of premature menopause.

Specific comments:

1. Line 24. Precise: Women with XP.....had reduced age at natural menopause (median 29.5 years). "Natural" menopause is a misleading term since these women underwent premature menopause. Natural menopause should be removed throughout the manuscript and just referred to as "menopause". Also, the median age of 29.5 years is misleading. This median age of menopause was calculated from 18 patients (n=18, line 37) who reported menopause. There are, it seems, women included in the study over the age of 40 who had not reported menopause at the time of the study. These women if included would clearly increase the median age of menopause for women with XP.

2. line 38. Premature menopause was present in 78% (14/18) and primary ovarian insufficiency was documented in 9 women. It is unclear if these 9 women are in addition to the 14 or if there is overlap of the groups.

3. Line 58. Mean age at natural menopause is 50+/- 4 years. Would leave out "natural".

4. Line 59. Primary ovarian insufficiency is defined as a woman under the age of 40 years with amenorrhea or irregular menses periods for 4 months plus two elevated FSH levels.... Clearly amenorrhea would indicate premature menopause. So do the authors group those women with premature menopause with patients having irregular menses and elevated FSH levels into the POI group? This is unclear in the manuscript.

5. Line 111. Women who were >9 years old at the time of last observation were included in the present study. (60 women) Why would 10 year old girls be included in this study? It makes it difficult to follow the numbers presented throughout the manuscript. Also, the two main outcome measures were menarche and menopause. In line 118, the authors write that there were 48 women age 18 to 60 years of age. Wouldn't it be more appropriate to only include these women since all would have been expected to have undergone menarche even if many hadn't undergone menopause?

6. Line 118. There were 48 women age 18 to 60 years (Figure 2). Line 120. Premature menopause was present in 14 (38%) of the 37 XP women under age 40 and normal age of menopause was present in only 4 (27%) of the 15 XP women age 40 or older. The numbers don't add up. 37 women under 40 plus 15 women over 40 is 52 women total. But the authors say that there are 48 women presented in Figure 2. Additionally, Figure 2 is difficult to interpret. This reviewer can only count 7 women represented by columns on the graph over 40 years of age.

7. Line 120. Premature menopause was present in 14 (38%) of 37 XP women under age 40. Therefore, it seems that 23 women had not undergone premature menopause. How could the median age of menopause for women with XP be 29.5 years when the majority of women had not undergone menopause by age 40?

8. Line 126. POI was documented in 9 women on the basis of 2 or more blood tests at least 4 months apart..... (Table 2). The information in Table 2 does not contribute to the paper and should be deleted.

9. Line 142. In this cohort of 60 XP women we report the finding of premature menopause. Again this cohort should be reduced from 60. Women under the age of 14 or 16 or 18 years of age (pick an age) should not be included.

10. Table 1 should be shortened considerably. One row for mean or median age, just pick one. One row for age range instead of 2 rows for youngest and oldest. No reason to present race/ethnicity. This is described in the text.

In general, it seems clear that XP women have an increased risk of premature ovarian failure/menopause and have earlier menopause in general. This is an important finding and the discussion emphasizes the need to properly counsel these women regarding decisions about reproductive choices and timing of child bearing. However, the presentation of the data is not clear.

Reviewer #3: This manuscript has new information that only an institution like the NIH can provide - the ability to study a rare disease (xeroderma pigmentosum) over an almost 50 year period of time. Even though the typical gynecologist will never see a patient with this genetic condition, it is still important new information in that it will allow more appropriate counseling regarding potential fertility.

The abstract is well presented.

The introduction importantly points out that because of improved treatments for the effects of this condition, more woman will live into their reproductive years.

The definition of menopause (line 58) is accurate but archaic. Today many women will have permanent cessation of menses without any loss of ovarian function, e.g. hysterectomy with ovarian preservation. These women are certainly not menopausal.

In the index case, did this woman receive any chemotherapy prior to age 27, the time of her last menses?
Does the IRB-approved natural history protocol cover deceased subjects? If a subject was at least 9 years of age but not yet reached menarche, was she included?

Line 130 contains the term "miscarriages" which is a lay term for spontaneous abortion. I would recommend using the medical terminology.

While the information in Table 2 is important, the table itself adds very little.

The most important clinical concern is contained in lines 173-175 and summarizes why practicing gynecologists need this information.

There are no "generalist obstetrician/gynecologists" (line 177), but "specialists in general obstetrics/gynecology."

Do you have permission to publish the photograph of the deceased subject in Figure 1?

Table 1 lacks descriptors of columns A through G (Complementation Groups).

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

This is a very interesting case series. It is limited by the understandable modest sample size, but also by the variable follow-up and age at evaluation for menopause/no menopause.

Specifically, among the women age 18-60 (N = 48), 18 (38%) had premature menopause and by age stratum, among those older than 40, 4/15 (27%) had premature menopause (Fig 2). Therefore estimating the median or mean age of menopause among women with XP is based on a biased sample. Only after all (or substantially all) women had reached menopause can one make such an estimate with any precision given a sample of this size. Alternatively, if longitudinal data were available from this cohort, one might use Cox proportional hazards or other methods to estimate the median age at menopause, but that also would be problematic given the sample size.

It is certainly reasonable to report the data and state that the rate of premature menopause is higher than the general population, but generation of curves, such as in Fig 4, is fraught with error since the cumulative percentages will certainly shift downward as the remaining women enter menopause. Specifically, Fig 4 is misleading in that it shows that 100% of women with XP experienced natural menopause by age 48, but that is only true for those who experienced menopause, not the 30 (48-18) women of age ≥ 18 who had not yet entered menopause.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- With revision of manuscript, please make sure you revise the abstract appropriately as well.
- define how subsets were chosen, characteristics.
- not sure what you mean by "had history". Please clarify
- please provide context. Is this data for the US? What year?
- Premature ovarian insufficiency and xeroderma pigmentosa, for instance, will need to be spelled out throughout the paper and abstract.
- why menarche? You have developed a nice case to this point of why you are looking for age of menopause, but this is the first time you mention menarche.
- while interesting, the index case is not needed in the manuscript and is not consistent with journal style.
- The first sentence here (starting line 83) can be rewritten since you tell us on line 84 what the IRB number and name are. Also, when you write that a study occurred between date 1 and date 2, it literally excludes those boundary dates. For instance, "This study was performed between Feb 2018 and Jan 2019" would mean it was performed from March 2018 to Dec 2018. Do you instead mean that the study was performed from date 1 to date 2? If so, please edit.
- how were they identified? Is there a data base? The time frame is beyond the time of electronic health records or computerized data bases. What was your data source you used to ID these women?
- The Journal style doesn't use the virgule (/) except in numeric expressions. Please edit here and in all instances.
- looked where? What evidence? Lab? symptoms? vaginal atrophy?
- you've defined premature menopause above-- it does not need to be redefined here.
- 37 XP women with XP needs to be edited
- It's hard to follow this. would you consider the following:

There were 48 women aged 18 - 60 years [is it 60 or 61? on line 111 you say ages up to 61? Why would you exclude the 61 year olds in this analysis?]. Of these, natural menopause was reported in 18/48 (38%), with age at menopause ranging from 18-38 years. Premature menopause occurred in 14/48 (29%). Among the 37 women in the cohort less than age 40 years, 14 (38%) had premature menopause. Among the 15 women age 40 years and older, 11(73%) reported premature menopause."

Its better to report the same outcome rather than flipping them--for the younger women you reported rate of premature menopause while for older women, you reported age at normal age.

- in total, you had 14 women < age 40 and 11 women > 40 with premature menopause for a total of 25 women w/ premature menopause if i'm reading this correctly. Why do you have mutation analysis on only 14? Which 14?
- report p values to only 3 decimals.
- you don't mention reproductive history in your methods. If you are going to report these, please add to the methods. As it is not the focus of your paper, I would probably just delete this section.
- report the disproportionate finding of premature menopause ?
- Now known as specialist obstetrician gynecologists, in distinction to subspecialists such as REI, MFM, etc.
- Do you have her consent or her family's consent to publish her picture? If not, it should be deleted.
- explain what a complementation group is please in the table title.
- please indicate that X axis is age.

2. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we

will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
- B. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

4. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:

- Lines 142-3 ("The age at the final...of aging and health").

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, tables, boxes, figure legends, and print appendixes) but exclude references.

7. Please orient the submission so that the manuscript pages are displayed in portrait mode, as opposed to landscape.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

13. Figures 1-3:

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

14. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

15. If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 27, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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