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)*

**The corresponding author has opted to make this information publicly available.*

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Date: Sep 13, 2019
To: "Anna Jo B. Smith" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1497

RE: Manuscript Number ONG-19-1497

The Effect of the Affordable Care Act on Women with Ovarian Cancer

Dear Dr. Smith:

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 Oct 04, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Precis - Under the Affordable Care Act (ACA) women with ovarian cancer are more likely to receive diagnosis at early stage and receive treatment within 30 days

Abstract: Purpose - Interventions at early diagnosis and treatment improve ovarian cancer outcomes - objective to evaluate ACA on stage at diagnosis and time of treatment
Methods - Rerospective cohort - stge at diagnosis and time to treatment before and after 2010 ACA - women 21-34 were the exposure group compared to women age 65+ (control)
2004-2015 data from the national cancer database - adjustments for urban versus rural, income status, comorbidities
Results - 41,038 - ovarian cancer pre ACA, 37,388 post ACA - increase in early diagnosis in the 21-64 year age group compared to 65+ and more receiving treatment within 30 days of diagnosis
women with public insurance and ACA had improvement in early stage diagnosis and treatment - this was seen across race and income
Conclusions - ACA - women more likely to be diagnosed and treated in 30d meaning ACA has long term impact in treatment as these are determinants of survival

Introduction - ovarian cancer, early diagnosis , and ACA introduced - objective: examine ACA's effect on stage, diagnosis, receipt of timely treatment, effect on racial, insurance and other socioeconomic disparities

Methods - Intervention group - 21-64 . affected by ACA; control group 65+ - Medicare - not affected; 2004-2009 - pre ACA and 2011-2015 - post ACA
National cancer database for data, pre and post-reform and early and late stages of aCA
1st outcome - insurance; 2nd outcome - early stage and diagnosis and 3rd outcome - treatment within 30 days
analyzed by insurance - public vs private, race, adjustments for income and education, etc

Results - ACA had a nonsignificant decrease in uninsured
early stage cancer increased in women 21-64 compared to 65+ and early diagnosis increased
ACA - incresed receipt of treatment in 30d , improvements more signfiicant in publicly insured, increase in early diagnosis and treament in white women and increase in treatment within 30 d in non-white women, and improvements at all income levels

Discussion - National cancer database used to show that after ACA there is increased likelihood in early stage diagnosis and early treatment
publicly insured women had larger gains and improvements in non white and low income women seen

Comments -
This is an appropriately done study and it is important to assess the role of ACA. It is important in showing that this does help minimize some of the healthcare disparities by showing improvements in non-white and low income women.

please proofread!
particularly lines 191 and 201 that say "was associated was associated"

line 193 - it says receipt of treatment within 30 days decreased in age 21-64 - do you mean increased? If not, this is incongruous with the rest of the manuscript

Reviewer #2: Thank you for this timely and pertinent work examining the association between healthcare reform, insurance status and ovarian cancer diagnoses.

This is a retrospective cohort study examining correlations between ACA and insurance and stage of disease at time of diagnosis of ovarian cancer. The manuscript is well organized and written clearly. The methods are appropriate, and the interpretation and conclusions are appropriately circumspect about causality.

I understand the rationale for the age groups corresponding to Medicaid and medicare populations, which would likely be disparately affected by ACA changes. However, there are also inherent differences in ovarian cancers diagnosed in these populations (21-64 v. >65 years), especially if "ovarian cancer" is not strictly defined as epithelial ovarian cancers.

Your results suggest there was an improvement in early stage at diagnosis in both of these groups before and after the ACA, though the differences are greater in the Medicaid-eligible group. It's a reasonable hypothesis that this is related to ACA-related implementations, but I think the discussion deserves mention of other possibilities, including more development of confounding variables between the two groups that could not be addressed by your study design.

I appreciate your explanation of difference-in-differences approach to your study design. I would also appreciate if you included context for how to interpret a DD of 2.5% so that your reader can understand both statistical and "clinical" or "practical" significance.

Reviewer #3: In this retrospective cohort study using data from the National Cancer Database between 2004-2015, the impact of the Affordable Care Act on stage of diagnosis and time to treatment for women with ovarian cancer was analyzed using difference-in-differences analysis. The intervention group was women ages 21-64 years (women affected by the ACA), while the comparison group was women ages 65 years and older (women eligible for Medicare throughout the study period and unlikely to be affected by the ACA). The study's conclusions were that under the Affordable Care Act, women with ovarian cancer were more likely to be diagnosed at an early stage and receive treatment within 30 days of diagnosis.

This is a very interesting topic and worthy of study. Below are the following questions.

1) The two groups being compared are inherently different in age, which cannot be changed given the effect of the ACA on these specific age groups. It is concluded that those in the intervention group (age 21-64) will have earlier stage of diagnosis. However those in younger age group will also have a higher proportion of specific types of ovarian cancers which inherently present in earlier stage, such as endometrioid ovarian cancers, clear cell carcinomas, germ cell tumors, low grade serous carcinomas. Please explain how this confounding has been managed in this analysis. Is it possible to control by histologic type of cancer.

2) How are borderline tumors classified in this database - are they included or excluded. Please clarify. If included, will also be a confounder.

3) It is known that younger women will have increased imaging for pelvic masses, which would lead to earlier detection of early stage disease, which is a lead-time bias. Explain how this is managed in the analysis, or should be commented upon.

4) The results section is very thorough but also very confusing to discern bottom line. There are multiple paragraphs that are written very similarly, including a typo of "was associated was associated" for late post-ACA difference-in -differences model, which looks like it was copy and pasted for repetitive paragraphs. There are also a multitude of tables and appendices that are difficult to read and decipher. Would suggest that the results section be re-written in a clearer way to make it easier for the reader to follow, and also be more selective in how the data is presented so that it is not a regurgitation of all results.

5) Primary outcome was insurance. Is it correct to interpret that there was no overall difference in insurance rates in the two groups? Why would that be, when ACA goal was to increase insurance rates in the intervention group? Also in the late

post-ACA model, there was a significant decrease in insurance? Lines 175-183 were confusing for this primary outcome result.

6) Second outcome was early stage of diagnosis - as alluded to in comment #1, could this be increased because younger age group is associated with specific histologic types of ovarian cancer that tend to present in early stage? Also, why would the late post-ACA model increase no longer be significant - over time, there's no longer a significant difference in detection?

7) Lines 203-241, there were multiple comparisons that were done for publicly and privately insured women, non-white and white women, and low-income women. These were all written very similarly and it was hard to follow. It was difficult to discern which results are statistically significant vs clinically significant. In large population-based studies, the outcomes may be statistically significant, but clinically the absolute change may not be relevant from a clinical point of view. Would re-write or shorten this section to make these paragraphs clearer as to what the overall message is, and to point out the results that are not only statistically significant, but also clinically significant. Given the number of comparisons, would the analysis need to be adjusted for the multiple comparisons.

8) Although it is presumed that earlier stage of diagnosis and earlier treatment within 30 days would result in increased survival, was a survival analysis done here? Could this be done with this data?

STATISTICAL EDITOR'S COMMENTS:

I suggest that the Authors should include figures showing the significant findings shown in Tables 2, 3, 4 and 5. Also, it would be helpful to include (could be separate Tables), how the difference in % corresponds to actual counts of the number of women in various categories (uninsured, low income, racial groups etc) who received early stage diagnosis, treatment within 30 days of dx. This could be based both on the data at hand (~ 70% of US cases, or extrapolated to estimates of entire US population during the time of this analysis.

EDITORIAL OFFICE COMMENTS:

1. 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. 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 point-by-point response letter.
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2. 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.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. 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.

5. 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, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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).

7. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

8. 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.

9. 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.

10. 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.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

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.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter.

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 Oct 04, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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Ref: ONG-19-1497 Title: The Effect of the Affordable Care Act on Women with Ovarian Cancer				
Comment Number	Reviewer's Comment	Authors' Response	Authors' edits	Page and Line number
1.1	please proofread! particularly lines 191 and 201 that say "was associated was associated"	We have edited the paper extensively to avoid potential typos.	N/A	N/A
1.2	line 193 - it says receipt of treatment within 30 days decreased in age 21-64 - do you mean increased? If not, this is incongruous with the rest of the manuscript	This is correct: the receipt of treatment within 30 days decreased from 92.8% to 91.1% among women ages 21-64 AND decreased 90.4% to 88.4% among women ages 65 years and older (unadjusted percentages). The difference-in-difference is significant because the change in the younger group was less than the change in the older group (and difference-in-difference analysis adjusted for additional sociodemographic factors). This ability to detect divergent trends between groups over time is one of the advantages of using a difference-in-difference model. We have expanded our methods section to clarify this. We have also edited the second paragraph of our results section to illustrate this.	"A positive difference-in-differences suggests that the ACA improved the outcome of interest; this may occur when the trend over time in the intervention and control group is positive/positive, negative/negative, positive/negative, or no change/negative because of greater differences over time in the intervention versus the comparison group. A difference-in-differences of zero suggests that there was no relationship between the ACA and the outcome of interest."	Page 6, Lines 155-160
2.1	I understand the rationale for the age groups corresponding to	We agree with the author about potential differences in histology	Methods: "For women with serous epithelial ovarian cancer, the ACA	Page 8, lines 242-

	Medicaid and Medicare populations, which would likely be disparately affected by ACA changes. However, there are also inherent differences in ovarian cancers diagnosed in these populations (21-64 v. >65 years), especially if "ovarian cancer" is not strictly defined as epithelial ovarian cancers. Your results suggest there was an improvement in early stage at diagnosis in both of these groups before and after the ACA, though the differences are greater in the Medicaid-eligible group. It's a reasonable hypothesis that this is related to ACA-related implementations, but I think the discussion deserves mention of other possibilities, including more development of confounding variables between the two groups that could not be addressed by your study design.	of ovarian cancer between younger and older women. This is why we conducted a subgroup analysis of only women with serous epithelial ovarian cancer. Similar to our overall analysis, we found significant improvements in receipt of treatment within 30 days of diagnosis for women with epithelial ovarian cancer. We have added to our methods and discussion section to discuss potential age-histology confounding.	was associated with significant increase in treatment within 30 days of diagnosis, including for non-white and low-income women." Discussion: "Histology of ovarian cancer differs by age with high grade serous ovarian cancer more common in older women and low grade serous ovarian cancer more common in younger women. Nonetheless, we found significant improvement in time to treatment and insurance status in our subgroup analysis of women with serous epithelial ovarian cancer under the Affordable Act."	244 Page 8, lines 277-280 Appendix Table 3
2.2	I appreciate your explanation of difference-in-differences approach to your study design. I would also appreciate if you included context for how to interpret a DD of 2.5% so that your reader can understand both statistical and "clinical" or	We have added the following to our discussion section to help readers with interpretation: "We estimate that, annually after the Affordable Care Act, around 100 more women ages 21-64 were diagnosed at early-stage and 70 more received timely treatment."	See left	Page 8, lines 249-251

	"practical" significance.			
3.1	The two groups being compared are inherently different in age, which cannot be changed given the effect of the ACA on these specific age groups. It is concluded that those in the intervention group (age 21-64) will have earlier stage of diagnosis. However those in younger age group will also have a higher proportion of specific types of ovarian cancers which inherently present in earlier stage, such as endometrioid ovarian cancers, clear cell carcinomas, germ cell tumors, low grade serous carcinomas. Please explain how this confounding has been managed in this analysis. Is it possible to control by histologic type of cancer?	See 2.1	“”	“”
3.2	How are borderline tumors classified in this database - are they included or excluded. Please clarify. If included, will also be a confounder.	Borderline cancers are included in the National Cancer Database, but were excluded from our analysis.	N/A	N/A
3.3	It is known that younger women will have increased imaging for pelvic masses, which would lead to earlier detection of early stage disease, which is a lead-time bias. Explain how this is managed in	We agree with the reviewer that lead-time bias is always a potential limitation in ovarian cancer studies. However, younger women were substantially more likely to be uninsured prior to the	N/A	N/A

	the analysis, or should be commented upon.	Affordable Care Act and thus unlikely to be receiving additional pelvic imaging prior to the Affordable Care Act. Thus, we do not think lead-time bias would have a substantial impact on our analysis.		
3.4	The results section is very thorough but also very confusing to discern bottom line. There are multiple paragraphs that are written very similarly, including a typo of "was associated was associated" for late post-ACA difference-in -differences model, which looks like it was copy and pasted for repetitive paragraphs. There are also a multitude of tables and appendices that are difficult to read and decipher. Would suggest that the results section be re-written in a clearer way to make it easier.	We have re-written the results section to make it clearer.	See results section.	Page 7, lines
3.5	Primary outcome was insurance. Is it correct to interpret that there was no overall difference in insurance rates in the two groups? Why would that be, when ACA goal was to increase insurance rates in the intervention group? Also in the late post-ACA model, there was a significant decrease in insurance? Lines 175-	Yes, there was no overall difference in uninsurance between the two groups. In the difference-in-differences model, there was an initial increase in uninsurance in the early post-ACA period and then a decrease in uninsurance in the late post-ACA period (e.g., more women had insurance after Medicaid expansion). These	Uninsurance did not change significantly for women ages 21-64 years post-ACA (p-for-trend=0.48) or for the comparison group of women ages 65 and older post-ACA (p-for-trend=0.08). In the overall difference-in-differences model, the ACA was associated with a non-significant decrease in uninsurance	Page 7, lines 176-184

	183 were confusing for this primary outcome result.	results are similar to prior analyses that found most of the ACA's insurance gains were later and from Medicaid expansion. We have re-written this paragraph of the results section to make it clearer.	(difference-in-differences=0.1%, 95% CI -0.3-0.5). In the early post-ACA model, the ACA was associated with a significant increase in uninsurance as insurance increased in the Medicare-eligible population (difference-in-differences=-1.3%, 95% CI -0.1-1.8). In the late post-ACA model, the ACA was associated with a significant decrease in uninsurance as insurance rates increased in women ages 21-64 years old and stayed the same in women ages 65 and older (difference-in-differences=-2.2%, 95% CI -2.7, -1.6).	
3.6	Second outcome was early stage of diagnosis - as alluded to in comment #1, could this be increased because younger age group is associated with specific histologic types of ovarian cancer that tend to present in early stage? Also, why would the late post-ACA model increase no longer be significant - over time, there's no longer a significant difference in detection?	See 2.1 for our discussion of the potential for confounding with age and histology.	""	""
3.7	Lines 203-241, there were multiple comparisons that were done for publicly and privately	We have rewritten the results section to clarify the findings and highlight clinically relevance. We	See, for example, discussion section, ""	Page 7-8

	insured women, non-white and white women, and low-income women. These were all written very similarly and it was hard to follow. It was difficult to discern which results are statistically significant vs clinically significant. In large population-based studies, the outcomes may be statistically significant, but clinically the absolute change may not be relevant from a clinical point of view. Would re-write or shorten this section to make these paragraphs clearer as to what the overall message is, and to point out the results that are not only statistically significant, but also clinically significant. Given the number of comparisons, would the analysis need to be adjusted for the multiple comparisons?	agree with the reviewer that focusing on the clinically significant change is important. To our knowledge, there is not a way to adjust difference-in-difference analyses for multiple comparisons.		
3.8	Although it is presumed that earlier stage of diagnosis and earlier treatment within 30 days would result in increased survival, was a survival analysis done here? Could this be done with this data?	We are not able to analyze survival as our maximum data was 5 years after the Affordable Care Act. We discuss this in the limitations section and hope to do this analysis when later year data is available.	"We plan on looking at long-term outcomes, including survival, once further follow-up data is available."	Page 9, lines 292-293
4.1 (Statistical editor)	I suggest that the Authors should include figures showing the significant findings shown in	Thank you for this suggestion. Please see Figures 1-2.	N/A	Figures 1-2.

	Tables 2, 3, 4 and 5.			
4.2	Also, it would be helpful to include (could be separate Tables), how the difference in % corresponds to actual counts of the number of women in various categories (uninsured, low income, racial groups etc) who received early stage diagnosis, treatment within 30 days of dx. This could be based both on the data at hand (~ 70% of US cases, or extrapolated to estimates of entire US population during the time of this analysis.	See 2.1. We extrapolated to the entire US population based on the estimate of the NCDB including 70% of new cancer diagnoses. Appendix Table 5 lists counts of ovarian cancer over time.	Appendix Table 5	Appendix Table 5