

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: May 07, 2019
To: "Saketh R. Guntupalli" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-367

RE: Manuscript Number ONG-19-367

Intrauterine Device Use and Ovarian Cancer Risk: A Systematic Review and Meta-analysis

Dear Dr. Guntupalli:

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 May 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: For the manuscript titled "Intrauterine device and ovarian cancer risk: A systematic review and meta-analysis", I have the following comments and queries:

1. There are a few grammatical errors in the manuscript. Please review it carefully for these needed revisions.
2. Please use the appropriate headings for the abstract and body of the manuscript.
3. Some of the information regarding other cancers and IUD use that is stated in the Introduction section would be better suited in the Discussion section.
4. The rigor of the literature search, the assessment of studies for inclusion, the analysis, the inclusion of a variety of different ethnic and socioeconomic groups, the scientific plausibility and the conclusions drawn seem appropriate.
5. Contacting authors for additional data and clarification is a strength of the study.
6. As this author's discuss, this study has the same weaknesses of any meta-analysis in which retrospective data is used, and the fact that the impact of the length of IUD use could not be studied.

Reviewer #2: The authors present a meta-analysis based on a systematic review of the literature reviewing the association between IUD use and ovarian cancer risk. While this has been addressed in the literature previously, this is the first meta-analysis, bringing together an international set of studies, and is generalizable because its lack of specified IUD type. Their findings demonstrate a significant odds ratio of 0.71 between ever use of IUD and ovarian cancer.

1) The authors exclude IUD use for menopausal hormone therapy. While there may not be many appropriate studies for their analysis, I would encourage them to consider the category of menopausal women too. Age is taken into consideration as a confounder, so these should still be valid results.

2) Figure 1 describes how 4 databases were searched to identify 16 articles for critical review. Why do the authors exclude articles before their Google Scholar search, and then why do they limit the search to the top 200 hits when they initially identified 399 articles from the databases? Why were the 2 articles from Google Scholar missed in the database search?

3) Is Table 4 suggesting that BMI and family history are also protective for ovarian cancer risk? I find that surprising? Unless I am reading the Table incorrectly?

4) Are the authors able to give any information about the duration of IUD use in these studies? For OCPs, use of 6 months may decrease ovarian cancer risk. If not available, please address this in the discussion as it is a practical consideration for cancer risk-reduction.

5) Do the authors have any additional information regarding the histologies of ovarian cancer identified? Might there be more of an effect on endometrioid tumors? We're non-epithelial tumors included in the papers reviewed as well?

6) Please soften the concluding sentence. The use of IUDs may decrease ovarian cancer incidence, which should decrease mortality, but to say that this may be a statistically significant decrease from a review / meta-analysis is over-reaching just a bit. The findings of this paper are interesting and worthy of dissemination however.

Reviewer #3: The topic of this meta-analysis is important, evaluating the impact of intrauterine contraception on ovarian cancer risk. The meta-analysis methodology is adequate, though it includes only 12 case control and cohort studies. However, there is a big problem of terms and this is my major concern. Intra Uterine Device (IUD) is not the same as levonorgestrel releasing Intrauterine Systems (LNG-IUS), as considered by the authors. They act with a completely different mechanism of action, copper vs. progestin release. I think that also the potential mechanism of ovarian cancer prevention may be completely different. The effect of a LNG-IUS 52 mg on the ovarian cancer reduction risk is mainly the prevention/reduction of retrograde menstruation and maybe the limited effect on the inhibition of ovulation during the first months of use (see Grandi G et al, Biomed Res Int 2015;2015:751571). Moreover, there are many different types of LNG IUS nowadays on the market (different doses), and the data herein reported are obtained only from LNG-IUS 52 mg, the highest dosage. In this sense, I think that this review has to be split in LNG-IUS 52 mg effect and copper IUD effect (different submeta-analyses), trying to understand if they have a similar effect and suggesting different potential mechanisms of action. Even if they are both called "intrauterine", they are two completely different contraceptive systems and it makes no sense to unify them.

Moreover, it is important on the other hand to discuss the concomitant effect of LNG-IUS on breast cancer risk, often associated with ovarian cancer in women with familiar risk (BRCA1-2 and other). There are many reports that start to show a positive association between LNG-IUS 52 mg use and breast cancer, mainly after long term use (see Soini T et al, Acta Oncologica 2016;55:188-192, Morch LS et al, N Engl J Med. 2017;377(23):2228-2239). This effect is not demonstrated for IUD.

STATISTICAL EDITOR:

Table 1 and lines 227-229: Not accurate to say that all these studies included age in their logistic regression models. Some matched by age, others included in adjustment. The summaries in Fig 2 should include those with age adjustment, not the crude ORs where age was not matched.

Fig 2: Some of the case-control studies have been matched by age, others were not, but were adjusted for age differences. It appears that the Authors included the crude, not the adjusted ORs in this series (eg, Ness, 2011, with aOR =0.8(.6-1.0) and Shu, 1989 with aOR=0.8(0.2-1.1). It also appears that the cohort studies from Dorjgochoo, 2009 and Huang, 2015 are both from the same Shanghai Women's Health study initiated from 1997-2000, but with differing follow-up reports. That is, these are not independent studies.

General: IUD use was stratified by "ever" vs "never" use, without any description of duration, time since cessation to OC diagnosis, or use of other contraception methods at times when the woman did not use IUDs for women with/without OC. That is, the use of "ever" IUD use may be confounded by other contraception methods which also were shown to be associated with less risk of OC. That is a particular concern if women later had BTL with salpingectomy, which would have altered their risk profile.

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, 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
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queries.

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.

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.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

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: Review articles should not exceed 25 typed, double-spaced pages (6,250 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. 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: Reviews, 300 words. Please provide a word count.

8. 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.

9. 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.

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"Fig 2: There is a lot of small text here, I'm worried that it'll be too hard to read on print. Please enlarge, is possible."

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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 May 28, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <http://ong.edmgr.com/login.asp?a=r>) Please contact the publication office if you have any questions.

May 27, 2019

Dear Editorial Board of the Green Journal,

Thank you for inviting us to revise our manuscript, Intrauterine Device Use and Ovarian Cancer Risk: A Systematic Review and Meta-analysis. Below, we provide responses to each of the reviewer comments. All comments are re-stated in bold, followed by our responses, along with the location of associated changes made to the manuscript. Line numbers reference the marked copy of the manuscript.

REVIEWER #1: For the manuscript titled "Intrauterine device and ovarian cancer risk: A systematic review and meta-analysis", I have the following comments and queries:

1. There are a few grammatical errors in the manuscript. Please review it carefully for these needed revisions.

Thank you for identifying these errors. We have done our best to address them.

2. Please use the appropriate headings for the abstract and body of the manuscript.

We have followed the recommended headings for a Systematic Review and Meta-analysis. From the Green Journal Instructions for Authors website, we found the following guidelines:

1) Abstract: Systematic review articles should have a structured abstract of no more than 300 words, using the following headings:

Objective: *Statement of purpose of the review.*

Data Sources: *Sources searched, including dates, terms, and constraints.*

Methods of Study Selection: *Number of studies reviewed and selection criteria.*

Tabulation, Integration, and Results: *Guidelines for extracting data, methods of correlating, and results of review.*

Conclusion: *Primary conclusions and their clinical applications.*

2) Headings: Review articles should be organized in a manner similar to their structured abstract.

Introduction: *Indicates why the topic is important and states the specific objective(s) of the review.*

Sources: *Identifies what was searched and how; if a computerized system was used, specify the dates searched, the language(s) covered, and the search terms used.*

Study Selection: *Identifies the number and nature of reports reviewed, the basis of any selection (ie, exclusion and inclusion criteria), and the reports in the final tabulation.*

Results: *Describes how observations across studies were tabulated and integrated into a cohesive whole.*

Discussion: *Includes what can be concluded from the exercise, along with clinical implications and need for additional research.*

3. Some of the information regarding other cancers and IUD use that is stated in the Introduction section would be better suited in the Discussion section.

Thank you for this observation. We have moved this section to an appropriate section of the discussion as you have recommended (Lines 363-370).

4. The rigor of the literature search, the assessment of studies for inclusion, the analysis, the inclusion of a variety of different ethnic and socioeconomic groups, the scientific plausibility and the conclusions drawn seem appropriate.

Thank you. We feel confident in our approach as well.

5. Contacting authors for additional data and clarification is a strength of the study.

Thank you. We felt it was critical to do our best to access all possible data.

6. As this authors discuss, this study has the same weaknesses of any meta-analysis in which retrospective data is used, and the fact that the impact of the length of IUD use could not be studied.

Yes, unfortunately these weaknesses are present, but a randomized control trial is not a feasible option for this type of data, and thus retrospective data collection is the best option available. Only a few studies evaluated duration of use and thus it did not feel significant enough to include in our analysis. We have addressed the inherent weaknesses of meta-analysis in the discussion section in detail (Lines 378-400)

REVIEWER #2: The authors present a meta-analysis based on a systematic review of the literature reviewing the association between IUD use and ovarian cancer risk. While this has been addressed in the literature previously, this is the first meta-analysis, bringing together an international set of studies, and is generalizable because its lack of specified IUD type. Their findings demonstrate a significant odds ratio of 0.71 between ever use of IUD and ovarian cancer.

1) The authors exclude IUD use for menopausal hormone therapy. While there may not be many appropriate studies for their analysis, I would encourage them to consider the category of menopausal women too. Age is taken into consideration as a confounder, so these should still be valid results.

Our concern with the menopausal hormone therapy studies is that these patients were often on a variety of other forms of hormones as well, which would confound the data. We revised the

manuscript to include this reasoning (line 165-167). If you feel strongly about this, we would be happy to consider re-evaluation of these studies. However we feel that adding this data would substantively alter the applicability of our conclusions given the confounders that would be introduced.

2) Figure 1 describes how 4 databases were searched to identify 16 articles for critical review. Why do the authors exclude articles before their Google Scholar search, and then why do they limit the search to the top 200 hits when they initially identified 399 articles from the databases? Why were the 2 articles from Google Scholar missed in the database search?

This is a reasonable concern. There is no standard approach for including a Google Scholar search, and even Cochrane does not require it for their systematic reviews (they do require Medline, Embase, and Cochrane Central, all three of which we included). Additionally, the Google Scholar search is not easily reproducible due to regular changes in search algorithms (as demonstrated in Bramer J Med Libr Assoc. 2016 Apr; 104(2): 143–145). Thus, our Google Scholar search was intended to be supplementary to the primary database review and only the top 200 results underwent title and abstract review.

The two articles that were missed in the database search did not contain the words “intrauterine device” in the title, abstract, or author provided key words.

We have made revisions in the manuscript to further clarify our reasoning and explain why the noted reports were missed in the database review (Lines 237-244). We hope this will help clarify the concern.

3) Is Table 4 suggesting that BMI and family history are also protective for ovarian cancer risk? I find that surprising? Unless I am reading the Table incorrectly?

For each of the studies we looked whether or not they addressed the given variables in their analysis, understanding that these variables could impact outcomes (ie a BTL could decrease the risk of ovarian cancer). Thus Table 4 looks at all the variables broken down by the studies that addressed them (or did not address them). Given that regardless of inclusion of this data, the summary ORs were inversely associated, we feel more confident that none of these factors were likely to have confounded the data.

Within this stratification, the summary OR was significant for stratification of studies based on covariates addressed. When considered the studies that did NOT address a given covariate, the studies that did not address BTL and family history still trended towards an inverse association, but was not significant.

4) Are the authors able to give any information about the duration of IUD use in these studies? For OCPs, use of 6 months may decrease ovarian cancer risk. If not available,

please address this in the discussion as it is a practical consideration for cancer risk-reduction.

Unfortunately, no. The vast majority of these studies looked only at never/ever use. Within the Shanghai Women's Health Study, Huang (2015) looked at benefit at more or less than 20 years of use and Dorjgochoo evaluated use greater than or less than 14 years of use, but they were the only authors that provided a time reference and we have subsequently removed the Dorjgochoo study. This "ever/never" approach is similar to how Cortessis et al (2017), who published in the Green Journal on IUD use and risk of cervical cancer had to present their data due to limited information on duration. It is discussed in the discussion on lines 385-387.

5) Do the authors have any additional information regarding the histologies of ovarian cancer identified? Might there be more of an effect on endometrioid tumors? We're non-epithelial tumors included in the papers reviewed as well?

Some of the studies provided data on the histology, but not substantial enough to analyze separately. The vast majority of the studies that did report histology were evaluating epithelial tumors. There was one study (Shu) that specifically reported that 7.4% were germ cell and 10.5% were sex cord stromal.

6) Please soften the concluding sentence. The use of IUDs may decrease ovarian cancer incidence, which should decrease mortality, but to say that this may be a statistically significant decrease from a review / meta-analysis is over-reaching just a bit. The findings of this paper are interesting and worthy of dissemination however.

Thank you. We have revised this sentence as you have suggested (Line 405-408)

REVIEWER #3: The topic of this metanalysis is important, evaluating the impact of intrauterine contraception on ovarian cancer risk. The meta-analysis methodology is adequate, though it includes only 12 case control and cohort studies. However, there is a big problem of terms and this is my major concern. Intra Uterine Device (IUD) is not the same as levonorgestrel releasing Intrauterine Systems (LNG-IUS), as considered by the authors.

Unfortunately, given the variety of intrauterine devices used throughout the world, including levonorgestrel IUDs, copper IUDs, Steal Rings, among others. We are looking simply at the concept of an intrauterine-based contraceptive device. We hypothesize that the intrauterine-nature of the device, regardless of whether it releases LNG or is simply copper, plays a role in the mechanism. See line 335-345. We also feel this is a benefit to the study, as when we consider a global community, the copper IUDs are far more prevalent and have the potential to have a broader impact. In the recent Green Journal study by Cortessis et al, the authors similarly were unable to separate out by type of IUD (LNG-IUS versus metallic).

They act with a completely different mechanism of action, copper vs. progestin release. I think that also the potential mechanism of ovarian cancer prevention may be completely different. The effect of a LNG-IUS 52 mg on the ovarian cancer reduction risk is mainly the prevention/reduction of retrograde menstruation and maybe the limited effect on the inhibition of ovulation during the first months of use (see Grandi G et al, Biomed Res Int 2015;2015:751571). Moreover, there are many different types of LNG IUS nowadays on the market (different doses), and the data herein reported are obtained only from LNG-IUS 52 mg, the highest dosage. In this sense, I think that this review has to be split in LNG-IUS 52 mg effect and copper IUD effect (different submetaanalyses), trying to understand if they have a similar effect and suggesting different potential mechanisms of action. Even if they are both called "intrauterine", they are two completely different contraceptive systems and it makes no sense to unify them.

We agree that it would be optimal to be able to separate the data based on the type of device used, but the majority of the reports reviewed do not include this information. Knowing the type of device could definitely provide insight into mechanism and allow for better guidance in use, but based on our review this data is not currently available.

Moreover, it is important on the other hand to discuss the concomitant effect of LNG-IUS on breast cancer risk, often associated with ovarian cancer in women with familiar risk (BRCA1-2 and other). There are many reports that start to show a positive association between LNG-IUS 52 mg use and breast cancer, mainly after long term use (see Soini T et al, Acta Oncologica 2016;55:188-192, Morch LS et al, N Engl J Med. 2017;377(23):2228-2239). This effect is not demonstrated for IUD.

We feel the exploration of the impact of the LNG-IUS on breast cancer is beyond the scope of this meta-analysis, especially given the recent publications mentioned by Soini and Morch. There are multiple additional confounders in that argument as well. The focus of the current manuscript is on the association between IUD as ovarian cancer.

STATISTICAL EDITOR:

Table 1 and lines 227-229: Not accurate to say that all these studies included age in their logistic regression models. Some matched by age, others included in adjustment. The summaries in Fig 2 should include those with age adjustment, not the crude ORs where age was not matched.

We appreciate this observation. We have updated our figures to include Figure 2, which demonstrates crude data (both forest and funnel plots) and Figure 3 which demonstrates all adjusted data (in forest and funnel plots). You will find that with the use of adjusted ORs, the inverse association remains with OR 0.85 (CI 0.76-0.95). We hope the addition of this analysis further bolsters our presentation of the data. Please see lines 283-287.

Fig 2: Some of the case-control studies have been matched by age, others were not, but were adjusted for age differences. It appears that the Authors included the crude, not the

adjusted ORs in this series (eg, Ness, 2011, with aOR =0.8(.6-1.0) and Shu, 1989 with aOR=0.8 (0.2-1.1).

Thank you for this consideration. We have since reviewed the adjusted ORs and have included that data in addition to the crude data from the studies. We have also re-reviewed all studies and included their age control method (matched vs statistical) and updated Table 1 to reflect these details. We have also included any additional adjustments in Table 1. As mentioned above, we have updated Figure 3 to include a version of the analysis with adjusted ORs.

It also appears that the cohort studies from Dorjgochoo, 2009 and Huang, 2015 are both from the same Shanghai Women's Health study initiated from 1997-2000, but with differing follow-up reports. That is, these are not independent studies.

Thank you for this critical observation. This was an oversight on our part, despite attempting to confirm differing populations in all studies. We have since removed the Dorjgochoo data from the manuscript (as it is the more remote data) and the OR is actually more significant at 0.68 [0.62, 0.75]. Please see line 222-224.

General: IUD use was stratified by "ever" vs "never" use, without any description of duration, time since cessation to OC diagnosis, or use of other contraception methods at times when the woman did not use IUDs for women with/without OC. That is, the use of "ever" IUD use may be confounded by other contraception methods which also were shown to be associated with less risk of OC. That is a particular concern if women later had BTL with salpingectomy, which would have altered their risk profile.

Yes, this is unfortunately a potential confounder within our data. However, all of the studies included OCP use in their multivariate analysis and many included history of BTL in their multivariate analyses. Thus our adjusted analysis should help to cover those potential confounders. We appreciate your concern and have addressed it in our discussion (Lines 383-385)

Thank you again for the opportunity to resubmit our manuscript. Input from the reviewers has allowed us to make a number of revisions, including clarification regarding confounders, additional analysis of adjusted ORs, and removal of a study with redundant population from analysis. We believe the result is an improved manuscript that we hope you will find suitable for publication. Please do not hesitate to contact me if you think there are further issues to address. We look forward to your response.

Sincerely,

Saketh R. Guntupalli, MD
Associate Professor and Vice-Chair for Clinical Affairs/Quality
Division of Gynecologic Oncology

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