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.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Dec 06, 2019
To: "Emily H Adhikari" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2072

RE: Manuscript Number ONG-19-2072

Syphilis in Pregnancy

Dear Dr. Adhikari:

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 Dec 27, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a Clinical Expert Series article reviewing clinical manifestations, management, and screening algorithms of syphilis in pregnancy, as well as providing future research directions. Considering the recent rise of rates of syphilis in pregnancy and of congenital syphilis both in the United States and in Europe, this is definitely an important topic that merits discussion.
Overall, this is a well written and scholarly organized manuscript that provides a good overview of the problem of syphilis in pregnancy.
A few comments:

A public health crisis
- Line 64-72: all the listed factors have a pivotal role in the increase of congenital syphilis cases observed in the United States over the last few years. However, it's important to highlight that approximately 50 percent of pregnant women with syphilis in the United States have been reported to lack traditional risk factors for the disease (Trivedi S, Williams C, Torrone E, Kidd S. National Trends and Reported Risk Factors Among Pregnant Women With Syphilis in the United States, 2012-2016. Obstet Gynecol. 2019;133(1):27). Please update this paragraph accordingly.

Clinical manifestations of syphilis
- Please specify that clinical findings of each stage of syphilis are not altered by pregnancy status.

Secondary syphilis
- Please specify that secondary syphilis occurs in approximately 25 percent of untreated patients, usually beginning six weeks to six months after the appearance of the chancre of primary syphilis.

Congenital syphilis in the neonate
- Please specify that transplacental transmission of T. pallidum can occur at any time during gestation but occurs with increasing frequency as gestation advances. Also, the risk of transmission decreases with increasing time since primary or secondary infection and is reported to be only 2 percent after four years.

Prenatal screening for syphilis
- Line 192-193: 'All pregnant women should be screened for syphilis is currently recommended for all pregnant women at the first prenatal visit or at first presentation to care'. Please correct the sentence.

Serologic testing: traditional and reverse screening algorithms
- Line 243: '...false positive rates are as high as 40-80% for treponemal immunoassays...'. What is the false negative rate for these tests?

- Please specify that on rare occasions both non-treponemal and treponemal tests can be falsely positive due to a different infectious etiology (e.g., endemic treponematoses such as bejel), or a non-infectious condition affecting the immune function (Ratnam S. Can J Infect Dis Med Microbiol 2005;16(1):45-51).
- Line 263: Please explain the 'prozone' reaction.

Treatment in pregnancy
- Line 317-320: Please specify that the rate of congenital infection ranges from 1 to 2 percent for the offspring of women adequately treated during pregnancy to 70 to 100 percent for the offspring of untreated mothers. Also, the WHO estimates that treatment reduces early fetal deaths or stillbirths by 82 percent, preterm or low birth weight by 65 percent, neonatal deaths by 80 percent, and clinical disease in infants by 97 percent (Blencowe H, et al. BMC Public Health. 2011;11 Suppl 3:S9).

Clinical response to treatment and the Jarisch-Herxheimer reaction
- Line 359-361: Please explain that symptoms of the Jarisch-Herxheimer reaction are thought to result from the release of large amounts of treponemal LPS from dying spirochetes and an increase in pro-inflammatory cytokine levels.

Serologic response to treatment
- Please specify that a four-fold decline in maternal nontreponemal serologic titers following treatment does not guarantee that fetal treatment has been adequate and, therefore, neonates should always be evaluated for congenital syphilis after delivery.

- Please provide a better-quality image for Figure 7 (Clinical evaluation for syphilis algorithms).

Reviewer #2: This is a review of syphilis in pregnancy to keep the health care providers updated and aware of this serious STD which is of public health concern.

There review includes good revision of different stages of syphilis infection reaching the congenital syphilis as well details of diagnosing syphilis, but some comments need to be addressed:
- There is need to show trends in terms of numbers if available and how much numbers increased or rates per 100,000. It's mentioned that percentages increased by 172% (line 59), details of numbers are needed.
- what are the high risk groups or specific social determinants of this infection?
-once the pregnant woman is diagnosed, you mentioned the counseling with pregnant woman about treatment, do you recommend a pre-treatment ultrasound?
- your recommendation about follow -up of infected woman is not clear. Although the reference mentioned in the section of follow-up is CDC, but being pregnant is not indication for close follow-up and frequent test every 4 weeks to check treatment failure or re-infection.

Reviewer #3: Thank you for this paper, as I have seen syphilis rise in our community and a lack of knowledge among younger OBGYNs and residents (a victim of our success?) this is very timely. It is also very nicely written.

Line 74: some debate about whether we are primary care physicians, I certainly consider myself a specialist. Perhaps " as primary care physicians for pregnant women"? Also, unless you are aiming to include other types of providers, I prefer physician to provider.

Lines 97-103: can you be more clear here, I felt like this read that immunocompetent host will clear syphilis and only immunocompromised will go on to develop secondary manifestations (which I know is not the case).

Can you give an estimate of what percentage of patients progress to tertiary or neurosyphilis? Is it everyone if given enough time, or do some stay in the late latent stage if untreated?

Line 192-3 needs to be re-written
Line 281: take out one "sequence"

PRODUCTION EDITOR: Please provide letters from those mentioned in the figure legends as providing the images as a courtesy. An email saying that they allow us to use the figure in print, online, and Spanish formats is sufficient.

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.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

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. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged, but should it be considered essential, written permission of the copyright holder must be obtained. Permission is also required for material that has been adapted or modified from another source.

Both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers now have online systems for submitting permissions request; please consult the publisher directly for more information.

When you submit your revised manuscript, please upload 1) the permissions license and 2) a copy of the original source from which the material was reprinted, adapted, or modified (eg, scan of book page(s), PDF of journal article, etc.).

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 short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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: Clinical Expert Series, 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. 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.

12. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

13. 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/ifauth.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.

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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 Dec 27, 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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UTSouthwestern
Medical Center

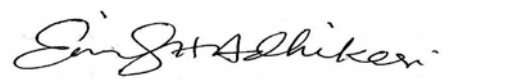
Manuscript Number ONG-19-2072
Syphilis in Pregnancy

Department of Obstetrics and

Dear Editors,

Thank you for the opportunity to revise and resubmit the Clinical Expert Series manuscript entitled *Syphilis in Pregnancy*. I am grateful for the thoughtful comments made by the reviewers. I have reviewed the Instructions for Authors in preparation of the revised manuscript.
As requested, below are the comments made by the reviewers and the editors, followed by my responses with line numbers corresponding to the location of revised text in the tracked version of the revised manuscript. With the revised manuscript submission, I have included the permissions letters for clinical images (in separate pdf files), as well as the compressed file containing a higher quality Figure 7.

Please let me know if you have any questions, and thank you for considering this revised manuscript for publication.



Emily Adhikari, MD

RESPONSES TO REVIEWER COMMENTS:

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1. A public health crisis
- Line 64-72: all the listed factors have a pivotal role in the increase of congenital syphilis cases observed in the United States over the last few years. However, it's important to highlight that approximately 50 percent of pregnant women with syphilis in the United States have been reported to lack traditional risk factors for the disease (Trivedi S, Williams C, Torrone E, Kidd S. National Trends and Reported Risk Factors Among Pregnant Women With Syphilis in the United States, 2012-2016. Obstet Gynecol. 2019;133(1):27). Please update this paragraph accordingly.

Response: Thank you for the insightful comment. I have added the following text with the above reference:
Lines 83-86.
Although risk factors such as multiple sexual partners or concomitant STI may be presumed, a recent examination of risk factors among pregnant women diagnosed with syphilis between 2012 and 2016 from the National Notifiable Disease Surveillance system demonstrated that almost half lacked traditional risk factors for the infection.(ref)

2. Clinical manifestations of syphilis
- Please specify that clinical findings of each stage of syphilis are not altered by pregnancy status.

Response: Thank you, I have revised the sentence to include the following:
Lines 98-100.
The myriad manifestations of this "Great Masquerador" are well described, are not altered by pregnancy status, and may be best understood within the context of the human immune response to T pallidum *infection (Table 1).*

3. Secondary syphilis
- Please specify that secondary syphilis occurs in approximately 25 percent of untreated patients, usually beginning six weeks to six months after the appearance of the chancre of primary syphilis.

Response: In most sources, the time frame for appearance of secondary manifestations states a range usually between 4 to 10 weeks after appearance of the chancre, which I have included in the revised text, as below. I also revised Table 1. (Timing of Diagnosis for Secondary Syphilis) for consistency.
Lines 128-129.
Secondary syphilis occurs in approximately 25% of untreated women, and clinical symptoms usually manifest between 4 to 10 weeks after the initial appearance of the chancre.

4. Congenital syphilis in the neonate
- Please specify that transplacental transmission of T. pallidum can occur at any time during gestation but occurs with increasing frequency as gestation advances. Also, the risk of transmission decreases with increasing time since primary or secondary infection and is reported to be only 2 percent after four years.

Response: Thank you for the comment. I have inserted the following:
Lines 187-190.
Although transplacental transmission of T pallidum can occur at any time during gestation, it occurs with increasing frequency as gestation advances. The risk of transmission decreases with increasing time since primary or secondary infection and is reported to be only 2% after four years.

5. Prenatal screening for syphilis
Line 192-193: 'All pregnant women should be screened for syphilis is currently recommended for all pregnant women at the first prenatal visit or at first presentation to care'. Please correct the sentence.
Response: Thank you, this typo has been corrected:
Lines 222-223.
All pregnant women should be screened for syphilis at the first prenatal visit or at first presentation to care.

6. Serologic testing: traditional and reverse screening algorithms
- Line 243: '…false positive rates are as high as 40-80% for treponemal immunoassays…'. What is the false negative rate for these tests?

Response: The sensitivity of most available immunoassays is around 95%-100.0% (see ref). I added the following line:
Lines 274-275.
The sensitivity of available treponemal immunoassays ranges between 97-100%, depending on clinical stage and the specific assay used.(ref)
Ref: Park IU, Fakile YF, Chow JM, Gustafson KJ, Jost H, Schapiro JM, et al. Performance of Treponemal Tests for the Diagnosis of Syphilis. Clin Infect Dis. 2019;68(6):913-918.

7. Please specify that on rare occasions both non-treponemal and treponemal tests can be falsely positive due to a different infectious etiology (e.g., endemic treponematoses such as bejel), or a non-infectious condition affecting the immune function (Ratnam S. Can J Infect Dis Med Microbiol 2005;16(1):45-51).
Response: I have added the line:
Lines 283-286.
On rare occasions, both non-treponemal and treponemal tests can be falsely positive as a result of previous exposure to a non-venereal endemic syphilis (i.e., yaws or bejel) or other infection causing a reactive treponemal immunoassay in a woman with false positive RPR.

8. Line 263: Please explain the 'prozone' reaction.
Response: I have added the text:
Lines 300-301.
(…prozone reaction, in which high antibody titers interfere with RPR test reactivity in the laboratory)…

9. Treatment in pregnancy
Line 317-320: Please specify that the rate of congenital infection ranges from 1 to 2 percent for the offspring of women adequately treated during pregnancy to 70 to 100 percent for the offspring of untreated mothers. Also, the WHO estimates that treatment reduces early fetal deaths or stillbirths by 82 percent, preterm or low birth weight by 65 percent, neonatal deaths by 80 percent, and clinical disease in infants by 97 percent (Blencowe H, et al. BMC Public Health. 2011;11 Suppl 3:S9).
Response: I have added the following line with above reference:
Lines 345-346.

Optimal treatment of syphilis during pregnancy is estimated to reduce the risk of congenital syphilis by 97%, stillbirth by 82%, preterm birth by 64%, and neonatal mortality by 80%.

10. Clinical response to treatment and the Jarisch-Herxheimer reaction
Line 359-361: Please explain that symptoms of the Jarisch-Herxheimer reaction are thought to result from the release of large amounts of treponemal LPS from dying spirochetes and an increase in pro-inflammatory cytokine levels.
Response: I have revised the following line to include the requested information:
Lines 403-405.
A systemic response involving increased circulating proinflammatory cytokines resulting from release of massive amounts of lipopolysaccharide (LPS) by dying spirochetes following treatment, the Jarisch-Herxheimer reaction typically occurs within the first 24 hours after treatment, and is more frequent among patients with early syphilis or high nontreponemal titers.

11. Serologic response to treatment
Please specify that a four-fold decline in maternal nontreponemal serologic titers following treatment does not guarantee that fetal treatment has been adequate and, therefore, neonates should always be evaluated for congenital syphilis after delivery.
Response: I have added the following text:
Lines 450-453.
Importantly, achievement of a fourfold decline in maternal nontreponemal serologic titers following treatment does not guarantee that fetal treatment has been adequate. For this reason, all exposed neonates should be evaluated for congenital syphilis after delivery.

12. Please provide a better-quality image for Figure 7 (Clinical evaluation for syphilis algorithms).
Response: This is provided in the uploads. Additionally, I have modified the text of the box under "Document early clinical stage and report to public health authorities" for clarity.

Reviewer #2: This is a review of syphilis in pregnancy to keep the health care providers updated and aware of this serious STD which is of public health concern.

There review includes good revision of different stages of syphilis infection reaching the congenital syphilis as well details of diagnosing syphilis, but some comments need to be addressed:

13. There is need to show trends in terms of numbers if available and how much numbers increased or rates per 100,000. It's mentioned that percentages increased by 172% (line 59), details of numbers are needed.
Response: I have added specific numbers to the text as follows:
Lines 63-65.
Between 2014 and 2018, primary and secondary syphilis in women increased by 172% (to 3.0 cases per 100,000 females) in the United States, and congenital syphilis rates have paralleled this rise, increasing by 185% (to 33.1 cases per 100,000 live births) in the same years.

14. What are the high risk groups or specific social determinants of this infection?
Response: Please see response to Reviewer #1 (Comment 1) above, and the following revised text:
Lines 83-86.
Although risk factors such as multiple sexual partners or concomitant STI may be presumed, a recent examination of risk factors among pregnant women diagnosed with syphilis between 2012 and 2016

from the National Notifiable Disease Surveillance system demonstrated that almost half lacked traditional risk factors for the infection.

15. Once the pregnant woman is diagnosed, you mentioned the counseling with pregnant woman about treatment, do you recommend a pre-treatment ultrasound?
Response: As described in lines 320-321, ultrasound findings of congenital infection are not typically manifest until after 18-20 weeks' gestation. Detailed sonography is considered before treatment when diagnosis is made near the threshold of fetal viability, as stated in lines 326-327. I have also added a reference to Figure 7 algorithm for added guidance:
Lines 337-340.
*Detailed sonography to evaluate for evidence of congenital syphilis is considered when maternal syphilis is diagnosed (**Fig.7**). In particular, targeted sonography is considered before initial treatment when maternal infection is diagnosed near the threshold of fetal viability.*

16. Your recommendation about follow -up of infected woman is not clear. Although the reference mentioned in the section of follow-up is CDC, but being pregnant is not indication for close follow-up and frequent test every 4 weeks to check treatment failure or re-infection.
Response: Thank you for the comment. Unfortunately, there are no concrete recommendations for follow up intervals in pregnancy. I have revised the following sentence to add clarity about clinical follow up:
Lines 459-460.
In all women, we inquire about partner treatment and potential for re-exposure at each prenatal visit following maternal diagnosis, and repeat an RPR at 28-32 weeks or sooner if the clinical history suggests re-exposure or reinfection.

Reviewer #3: Thank you for this paper, as I have seen syphilis rise in our community and a lack of knowledge among younger OBGYNs and residents (a victim of our success?) this is very timely. It is also very nicely written.

17. Line 74: some debate about whether we are primary care physicians, I certainly consider myself a specialist. Perhaps " as primary care physicians for pregnant women"? Also, unless you are aiming to include other types of providers, I prefer physician to provider.
Response: Thank you for the comment. This line has been revised to the following:
Line 89.
As primary care providers for pregnant women,…

18. Lines 97-103: can you be more clear here, I felt like this read that immunocompetent host will clear syphilis and only immunocompromised will go on to develop secondary manifestations (which I know is not the case).
Response: See response to Reviewer #1 (Comment 3). The following sentence has been added for clarity:
Lines 128-129.
Secondary syphilis occurs in approximately 25% of untreated women, and clinical symptoms usually manifest between 4 to 10 weeks after the initial appearance of the chancre.

19. Can you give an estimate of what percentage of patients progress to tertiary or neurosyphilis? Is it everyone if given enough time, or do some stay in the late latent stage if untreated?
Response: The following text has been added for clarity:

Line 169.
Tertiary syphilis, which occurs in up to 40% of individuals with untreated syphilis, refers to benign gummas and cardiovascular syphilis,…

20. Line 192-3 needs to be re-written
Response: This line was corrected, thank you. See Reviewer 1 (Comment 5)
Lines 222-223.
All pregnant women should be screened for syphilis at the first prenatal visit or at first presentation to care.

21. Line 281: take out one "sequence"
Response: One “sequence” was removed:
Line 319.
The complete genome of T pallidum was sequenced in 1998.

22. PRODUCTION EDITOR: Please provide letters from those mentioned in the figure legends as providing the images as a courtesy. An email saying that they allow us to use the figure in print, online, and Spanish formats is sufficient.
Response: These emails have been provided for each individual in pdf format.

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:
Response: A. OPT-IN: Yes, please publish my point-by-point response letter.