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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: 11/14/2022
To: "Mar Ramirez" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1640

RE: Manuscript Number ONG-22-1640

Monkeypox Cervical Disease: A New Challenge for Gynecologists

Dear Dr. Ramirez:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, and STATISTICAL EDITOR COMMENTS (if applicable) below.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 12/05/2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* Figures: Please remove letter labels. These will be added back per journal style. Please upload as figure files on Editorial Manager.

REVIEWER COMMENTS:

Reviewer #1: I have reviewed your case report in detail. Your clinical photographs are impressive.

Reviewer #2:

Review of Manuscript ONG-22-1640 "Monkeypox cervical disease: A new challenge for gynecologists"

A case report claiming primacy in terms of reporting cervical involvement, in addition to vulvar involvement, with lesions ultimately found to be secondary to monkeypox has been submitted. The author describes the case of an individual presenting with both vulvar and cervical lesions. They describe the assessment, diagnosis and ultimate resolution of the presentation.

Title - Perhaps a bit misleading as the patient had cervical and vulvar lesions.

Précis - A bit of an over statement perhaps if this is the first reported case of cervical involvement.

Abstract - Lines 6&9 - MP is not a standard abbreviation so would just spell out.

Teaching points - #3 does identification prevent transmission?

Introduction - Minor issue but spacing is unusual with multiple very short 1-2 sentence paragraphs.
Line 35 - Historical from when exactly?

Case - I would presume most individuals in Spain less than 30 are also not vaccinated against smallpox?
Line 65 - What lead to the inclusion of MP in your differential and thus the testing? Local rates of infection?
Line 74 - Please revise to make more prosaic rather than the use of the ":".
Line 87 - In general how long for lesions to resolve? After that time is it safe to resume sexual activity or is additional time needed?
Line 93 - What is meant by controls?
Line 96 - What were these results? Negative?

Discussion - Line 105/6 - Do these cases not include women with vulvar involvement and thus not anecdotal?
Line 148 - Considering noting this is a historical study regarding protection from Monkeypox by smallpox vaccination.

Tables - None

Figures - Fairly high-quality images. Not sure you need 3 images of the cervix in Figure 2.

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Sincerely,
Vivian W. Sung, MD, MPH
Deputy Editor, Gynecology–Elect

The Editors of Obstetrics & Gynecology

_____

Mar Ramírez MD, PhD
Gynecology Oncology Unit
Institute of Women's Health
San Carlos Clinical Hospital, Madrid
Complutense University of Madrid, Spain

27th November 2022

Dear Dr. Jason D. Wright

I am pleased to submit this Case Report entitled "**Monkeypox Cervical and Vulvar Disease: A New Challenge for Gynaecologists**" to be considered for publication in your prestigious Journal.

Since the start of the current monkeypox outbreak in May 2022 to date (September 13, 2022) 23,465 confirmed cases of monkeypox have been reported in Europe, of which 6,947 were in Spain. Between 92-98% of cases have been reported in men who have sex with men (MSM).

The cases of monkeypox reported to date in women are anecdotal (1-3%), and in those with genital involvement, only vulvar lesions are described. Involvement of the cervix, as in this case, is possible, making it necessary to perform a thorough gynaecological examination in these patients. The differential diagnosis of other pathologies and STIs with lesions secondary to monkeypox infection in the lower genital tract of women is therefore a new challenge for gynaecologists.

To our knowledge, this is the first case described in the literature of concomitant genital involvement of the cervix and vulva by monkeypox. Given the current epidemic outbreak situation, correct identification of these lesions is essential for proper disease control.

This is an original article that has not been published nor is it being evaluated by any other scientific journal. Therefore we believe this is an article that will be of great interest to your readers.

Thank you for your consideration of this manuscript.

Sincerely yours,

Mar Ramírez

EDITOR COMMENTS:

Please note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

* **Figures: Please remove letter labels. These will be added back per journal style. Please upload as figure files on Editorial Manager.**

We would like to thank you for your review. As you ask, we have deleted the letter labels from the images and we have uploaded as figures files on Editorial Manager.

REVIEWER COMMENTS

POINT BY POINT

- Reviewer #1: I have reviewed your case report in detail. Your clinical photographs are impressive.

We would like to thank you for your review. We appreciate your comment and positive feedback.

- Reviewer #2:

Review of Manuscript ONG-22-1640 "Monkeypox cervical disease: A new challenge for gynecologists"

A case report claiming primacy in terms of reporting cervical involvement, in addition to vulvar involvement, with lesions ultimately found to be secondary to monkeypox has been submitted. The author describes the case of an individual presenting with both vulvar and cervical lesions. They describe the assessment, diagnosis and ultimate resolution of the presentation.

We would like to thank you for your review. Let us add some comments to justify the approach of our case report.

Title* - *Perhaps a bit misleading as the patient had cervical and vulvar lesions.

RE: Thank you very much for your suggestion. According to your comments we have modified the title.

"Monkeypox Cervical and Vulvar Disease: A New Challenge for Gynecologists"

Précis - ***A bit of an over statement perhaps if this is the first reported case of cervical involvement.***

RE: Let us add some information to justify this point

According to articles published to date, the recent outbreak, have started abnormally, with lesions in the vaginal and perianal region but no subjective fever or other prodromal signs[1,2,3]. The identification of this lesions is not common, however; it is an important for outbreak containment.

As you suggested we have modify the word "essential" for "important".

PRÉCIS: Identifying the monkeypox lesions that may affect the lower genital tract in women is an important part of achieving proper control of the disease.

1. *Minhaj F.S., Ogale Y.P., Whitehill F., Schultz J., Foote M., Davidson W., Hughes C.M. Monkeypox response team 2022. Monkeypox outbreak – nine states, may 2022. MMWR Morb. Mortal. Wkly. Rep. 2022 Jun 10;71(23):764–769. doi: 10.15585/mmwr.mm7123e1*

2. *https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393*

3. *Tarín-Vicente EJ, Alemany A, Agud-Dios M, Ubals M, Suñer C, Antón A, Lancet. 2022;400(10353):661. Epub 2022 Aug 8.*

Abstract **-** ***Lines 6&9*** **-** ***MP is not a standard abbreviation so would just spell out.***

RE: Thank you for your appreciation, we have spelled it out in the text.

Teaching points **-** ***#3 does identification prevent transmission?***

RE: Thank you for your question. Let us add some information to justify this point

- According to the World Health Organization recommendations, "Surveillance and rapid identification of new cases is critical for outbreak containment. During human monkeypox outbreaks, close contact with infected persons is the most significant risk factor for monkeypox virus infection"
  https://www.who.int/news-room/fact-sheets/detail/monkeypox

- Prevention and control of human monkeypox rely on raising awareness in communities and educating health workers to prevent infection and stop transmission. *https://www.who.int/health-topics/monkeypox#tab=tab_3*

- Ongoing investigation suggests person-to-person community transmission, and CDC urges health departments, clinicians, and the public to remain vigilant, institute appropriate infection prevention and control measures, and notify public health authorities of suspected cases to reduce disease spread. Public health authorities are identifying cases and conducting investigations to determine possible sources and prevent further spread. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.
  Minhaj F.S., Ogale Y.P., Whitehill F., Schultz J., Foote M., Davidson W., Hughes C.M. Monkeypox response team 2022. Monkeypox outbreak – nine states, may 2022. MMWR Morb. Mortal. Wkly. Rep. 2022 Jun 10;71(23):764–769. doi: 10.15585/mmwr.mm7123e1

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Introduction ***- Minor issue but spacing is unusual with multiple very short 1-2 sentence paragraphs.***

RE: Thank you for your appreciation. We have structured the text this way to ease the reader comprehension, however we understand and accept that this may be modified on the final text.

Line 35 - Historical from when exactly?

RE: The use of this word may induce to a mistake. As you suggested we have changed the word "Historical" for "In epidemic outbreaks previus to this one".

Case - I would presume most individuals in Spain less than 30 are also not vaccinated against smallpox?

RE: As you said, in Spain most people under 30 are not vaccinated against smallpox. In 1979 the vaccine stop being mandatory.

https://www.boe.es/buscar/doc.php?id=BOE-A-1979-26365

Line 65 - What lead to the inclusion of MP in your differential and thus the testing? Local rates of infection?

RE: Our Hospital has a reference unit in sexual transmission infections in Spain. After the outbreak, several women were diagnosis with vulvar lesions due to Monkeypox. In this pacient he macroscopic aspect of these lesions, the age, the Human Papillomavirus vaccination and negative screening of cervical cancer orientated the lesion to be secondary to a sexual transmission infection, including the differential diagnosis for Monkeypox.

Line 74 - Please revise to make more prosaic rather than the use of the ":".

RE: Thank you for your suggestion. We have made the change.

PCR for monkeypox virus DNA was positive in both samples (cervix and vulva); cultures were negative; STI Multiarray-PCR was negative; serologic tests were negative for current infection but showed previous contact with Herpes simplex 1-2 (IgG), Epstein-Barr virus (EBNA-IgG), Mycoplasma pneumonia (IgG), and Chlamydia pneumonia (IgG).

Line 87 - In general how long for lesions to resolve?

RE: Persons with monkeypox should be considered infectious until all lesion scabs have fallen off and re-epithelialization has occurred, which typically lasts two to four weeks.

United States Centers for Disease Control and Prevention. Isolation and prevention practices for people with monkeypox. https://www.cdc.gov/poxvirus/monkeypox/clinicians/isolation-procedures.html (Accessed on October 31, 2022).

In our paciente it took two weeks to resolve.

To clarify we have included on the text the next sentence "At two weeks evaluation the vulvar lesion was resolved ".

After that time is it safe to resume sexual activity or is additional time needed

RE: According to your suggestions we have included the next line:

"Following the WHO recommendations, the patient was indicated to use condom during any sexual activity for 12 weeks after recovery"

Line 93 - What is meant by controls?

RE: It means medical visit. It was a misunderstanding in the translation. We changed the word in the text.

According to the WHO recommendations, the patient was indicated to use condom during any sexual activity for 12 weeks after recovery. Seven days after the last medical visit, during the follow-up examination, patient was asymptomatic. Physical exam showed the cervical lesion disappearance and an almost complete resolution of the vulvar lesion. (FIGURE 4) At two weeks evaluation the vulvar lesion was resolved. Further medical visits were also carried out at 15 and 30 days, both confirming the complete resolution of the lesions.

Line 96 - What were these results? Negative?

RE: The results were negative.

We have change the text for better understanding:

"Additionally, serology was carried out at 1 month and 3 months from initial appearance,

ruling out HIV and viral hepatitis, respectively".

Discussion - Line 105/6 - Do these cases not include women with vulvar involvement and thus not anecdotal?

RE: In cited articles the do not specify the percentage of women with vulvar lesions, however on the WHO most recent data from November 16th 2022 a 23,7% had a genital rash.

https://worldhealthorg.shinyapps.io/mpx_global/#1_Overview

As of November 16 2022

	All	Male	Female
Any rash	28,180 (85.5%)	26,832 (85.9%)	738 (73.0%)
Systemic rash	19,715 (59.8%)	18,884 (60.4%)	658 (65.1%)
Fever	19,143 (58.1%)	18,246 (58.4%)	527 (52.1%)
Genital rash	15,154 (46.0%)	14,461 (46.3%)	240 (23.7%)
Headache	10,379 (31.5%)	9,709 (31.1%)	422 (41.7%)
Any lymphadenopathy	9,801 (29.7%)	9,602 (30.7%)	183 (18.1%)
Fatigue	9,622 (29.2%)	8,960 (28.7%)	318 (31.5%)
Muscle ache	9,230 (28.0%)	8,658 (27.7%)	331 (32.7%)
General lymphadenopathy	7,265 (22.0%)	7,129 (22.8%)	132 (13.1%)
Local lymphadenopathy	6,547 (19.9%)	6,421 (20.5%)	113 (11.2%)
Sore throat	4,545 (13.8%)	4,207 (13.5%)	168 (16.6%)
Rash, unknown location	3,315 (10.1%)	3,292 (10.5%)	20 (2.0%)
Oral rash	2,901 (8.8%)	2,404 (7.7%)	59 (5.8%)
Chills	2,794 (8.5%)	2,391 (7.7%)	96 (9.5%)
Vomiting	705 (2.1%)	656 (2.1%)	46 (4.5%)
Other	78 (0.2%)	75 (0.2%)	3 (0.3%)
Asymptomatic	32 (0.1%)	31 (0.1%)	1 (0.1%)

Line 148 - Considering noting this is a historical study regarding protection from Monkeypox by smallpox vaccination.

RE: Totally agree with your comment. The WHO uses this same percentages in their data, so we have updated the bibliography for a more recent one and we have modified the next sentence:

"Vaccination against smallpox was demonstrated through several observational studies to be about 85% effective in preventing monkeypox."
World Health Organization. Monkeypox. Vaccination. Accessed on November 21, 2022

https://www.who.int/news-room/fact-sheets/detail/monkeypox

Tables - None

Figures - Fairly high-quality images. Not sure you need 3 images of the cervix in Figure 2.

RE: Thank you for your appreciation. We had included 3 images because we considered that in this case the iconographic documentation is very important. That why we included the image of the cervical lesion, another one with more amplification and a third image with the Schiller Test.

However, if you considered that is not necessary to include the 3 images, we can deleted the amplify one (figure 2 D).

We hope that we have provided enough detail for you to reconsider publishing our manuscript, and we remain at your disposal for any further clarification you may require.