OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: Aug 17, 2020
To: "Sowmya Sunkara" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2095

RE: Manuscript Number ONG-20-2095

CHROMOPERTUBATION OF ECTOPIC PREGNANCY: A CASE REPORT

Dear Dr. Sunkara:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Sep 16, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review this manuscript. This is an interesting case report and it is well written. The authors of this manuscript described a case of ectopic pregnancy which chromopertubation was used resulting in expulsion of tubal pregnancy. This is a challenging clinical scenario as the patient desired to preserve future fertility. Often times, patients in similar scenario are counseled about the need to remove of the effected tube and they may have to pursue IUI as an alternative for future pregnancy. The dilemma is that patient may come back with another ectopic pregnancy and need for an additional surgery.

Here are my comments and questions:

1) The incidence of ectopic pregnancy increases three to eight folds in patients who had prior ectopic pregnancy. As it is mentioned in this case she had one prior ectopic pregnancy and salpingectomy in the contralateral tube. Do you have more information regarding patient's past history such as STI, endometriosis and any other pelvic surgery? I think it is important to describe clinical presentation in details

2) Line 54, 55: You mentioned " Chromopertubation…. an alternative treatment to surgical removal of the tube or damaging fallopian tube". She had patent fallopian tube in the OR, Did you consider HSG 3 months postoperatively to confirm tubal patency? My concern is the underlying pathology she may have had resulting in two ectopic pregnancies. It is also hard to exclude the tube is intact even after expulsion of ectopic pregnancy and there is no residual damage as there is no data to support this claim.

3) Line 91, What was the patient's Hematocrit? The clinical presentation described a stable patient with no major drop in her Hemoglobin and normal vital signs. The ultrasound finding appeared as a ruptured pregnancy! Did you consider observation and serial H&H given the fact that patient strongly desired future fertility?

4) Please describe the location of ectopic pregnancy in the tube.
5) Did you go to the OR with the intention of using chromopertubation in for expulsion of this ectopic or to ensure the presence of left tube? Please clarify in your manuscript.

6) Lines 156, 157: Please describe the multiple factors that need to be taken into account regarding management options.

7) I suggest labeling your figures as it helps the reader to orient and better appreciate the location of the pregnancy in the tube.

Reviewer #2: Thank you for the opportunity to review your work. As a MIGS surgeon, I was really excited to read this report! To the best of my knowledge, I could not find any case reports or descriptions of such technique. Pure genius!

I have some questions and comments below

1. Images and video
a. Do you have any other photos aside from what you have? They are quite limited-before and after pic, but none showing how it was done (i.e. no in-between). Do you have those "in-between" pics? If yes, please add.
b. Video-for a novel technique like this a video would be a make or break it, and it would have all the details of how you did it so that others could watch for details in order to replicate it. Do you have a video? If yes, please add.

2. Related surgical technique
a. Please add reference below to your text. Although they use vasopressin injection instead of chromotubation it is same idea.

https://surgeryu.com/detail/1045
Tubal Flushing A Novel Treatment Modality for Ectopic Pregnancy
Jayakrishnan K Krishna Pillai,MDDivya S Nambiar,MD
b. Please comment why you did not inject vasopressin into the tube first
a. That would help you with hemostasis in case it bleeds from ectopic site
b. How would you address bleeding if it did not stop after flushing?
i. Maybe inject topical fibrin agents into the tube?
ii. Other thoughts?
c. Tubal flushing
a. As been studied for subfertility, please add to your discussion/intro as it seems to be relevant
b. Consider putting "tubal flushing via chromotubation" into your title as that might make it clearer
d. Tubal milking
This technique has been described in conservative management of ectopics. Please add references and incorporate into intro/discussion.

3. How did you think of this technique? What made you think it was feasible? Please explain how you came up with this idea

4. Tubal flushing w/chromotubation vs. salpingostomy. How did you make this decision intraop?

5. Teaching points need to be revised.
a. 1st teaching point is too strongly worded-this is only proof of concept and you can't say anything about damage or fertility outcomes at this point
b. 2nd point is a bit off. Would it be better to say that it might be alternative other tube-sparing techniques?

6. Case details
a. Was there an signs intraop that ectopic was aborting? Description on line 107 sounds like aborting ectopic.
b. Lines 58-73 need to be re-written to take focus off ectopic reviews and to focus on existing tube sparing options.
c. Edit entire report for style, spelling and grammar.
i. Ex line 79. "gravida three, para 1" is odd. "gravida 3, para 1"?
ii. Ex. line 77 "therefore"
d. Line 77. Did you obtain consent from patient for publication of this report and for use of images?
e. Lines 79-89 can be condensed, and redundancies removed to retain the following facts
i. Pt strongly desired childbearing
ii. She was not able to afford ART and having her tubes was he only hope
iii. She was willing to accept higher risk of recurrent ectopic with tubal conservation and need to follow betas serially with potentially needing MTX for retained POCs
iv. She did not have her op reports and recalled that she had salpingostomy on one side but did not know which.
v. Patient had eval at outside clinic but did not have records and entire eval was reported in the ED.
f. Lines 105. Please describe
i. exact location in the tube (which portion-ampulla?)
ii. size in cm of ectopic
iii. presence or absence of tubal damage
iv. Why did you use Kahn canula instead of a Humi? The latter could theoretically generate more pressure.

7. Lines 126-130. Other techniques involve use of vasopressin, microelectosurgery, and topical fibrin products (floseal) to achieve hemostasis

8. Consent. Given that you decided to utilize this novel technique, how did you counsel pt. on this preop?

9. Lines 146-148. Given that this is only report describing this, I would re-write that you need to consider safety issues and candidate selection I future work, but not state your ideas as recs.

10. Line 157. What are "special populations" are you referring to? Those who cannot afford IVF? That gets to reproductive justice issues…

11. What would be next steps in studying this further?

Reviewer #3: The article is a case report of surgical technique involving chromopertubation to expel a tubal ectopic pregnancy. It is a fascinating idea and I feel (following substantial revision) this article can change management of certain patients.

I have multiple questions/comments regarding the manuscript (the first number is a line to which the comment is most appropriate). I also suggest an English language editor to review the article.

58 - cervical pregnancy is also considered ectopic, please modify definition (e.g. outside of normal location of endometrial cavity)

59 - please mention that treatment option depends on location

62 - instability - replace

64-65 - laparotomy as a method of choice is relatively remote history

67 - salpingostomy vs salpingotomy - I am not clear on the difference, the reference you providing (ACOG PB #193) doesnt' distinguish these procedures.

In general in introduction section I would suggest to add a brief overview of comparative fertility outcomes among patients undergoing various treatment options of tubal ectopic (MTX, salpingostomy, salpingectomy). I would also suggest reviewing the concern of prior tubal damage as a main risk factor for ectopic pregnancy.

74 - please briefly describe chromopertubation in introduction section

81 - invention?

85-87 - I am not sure description of positive pregnancy test result and absent records of current pregnancy are clinically relevant in this case

91 - it would be nice, but not necessary to have sonographic images

108 - I am not aware of the verb "chromopertubate" - perform chromopertubation

109-114 - I admire your honest description of the technique - it seemed you basically stumbled upon it by accident - this is just great.

Discussion - again, your main point seems to be preservation of fertility, therefore I would recommend stressing that aspect in your discussion rather than description of salpingectomy/salpingostomy which you did not (fortunately) perform in this case.

In my personal experience doing chromopertubation during surgery for EP is somewhat difficult - probably due to tubal or endometrial edema. Can you please address that? Are there any studies of chromopertubation during surgeries for ectopic (after salpingectomy)?

The article by Decherney is from 1985 - are there any more recent references on the subject?

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and

reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

I'm going to be making some substantial recommendations to make your paper more succinct and focused. Please make sure that my suggestions reflect the truth and emphasis you wish to express.

43. "tubal damage" seems a bit oblique to me. I believe what you are referencing here is salpingostomy with risks of tubal scarring. Would you consider saying here, and elsewhere that you use "tubal damage" "..."either salpingectomy or salpingostomy with risk of tubal injury"?

44. Rather than say "the following case", consider something like "A patient with a prior ectopic pregnancy in the left tube presented with an ectopic in the right one. As the patient strongly desired future fertility and the intraoperative status of the right tube could not be confirmed, chromopertubation was performed and incidentally, the ectopic pregnancy was expelled from the right tube".

This is a little clearer and is an important focus for your revision. As the full paper is written, it is clear that you did not perform the chromopertubation for the purpose of flushing the tube w/ the ectopic. This was all incidental or serendipitous and needs to be presented as such throughout.

52. Even in patients who don't strongly desire future fertility, these surgeries can cause damage or impair fertility. Perhaps " Salpingectomy and salpingostomy done for surgical management of ectopic pregnancy may impair future fertility".

54. Perhaps "Chromopertubation of an unruptured ectopic pregnancy under laparoscopic visualization may be an alternative to salpingectomy or salpingostomy".

I do think its important to add the information that this was not done blindly. You are proposing an interesting alternative. Most people will only read the abstract and teaching ponts so this needs to be clear. Third teaching point would be "Follow up patients treated with chromopertubation is important to assess for future fertility and potential complications of this treatment".

Please number the 2 teaching points.

58: perhaps "Approximately 2% of pregnancies in the United States are ectopic, with implantation outside of the uterus and most commonly in the fallopian tube" is better?

63. Aren't there also contraindications such as size of the ectopic, presence of a fetal heart beat?

64. Delete lines 64-66. You can just say "Surgical management includes laparoscopic salpingostomy, salpingotomy or salpingectomy. While surgically successful for treatment of the ectopic pregnancy, these approaches can result in impaired fertility and tubal scarring. As such, with a recurrent ectopic in the contralateral tube, surgical planning must be tailored to incorporate the patient's desire for future fertility"

Please also add a reference for the actual data (which should be included) o

74. "The case to follow describes a potential alternative approach to remove a tubal ectopic pregnancy without surgical intervention of the fallopian tube. " Delete sentence starting w/ "IRB approval...".

79-91: this can be made much more succinct: "The patient is a 35 year old, G3 P1011 seen in the emergency room for vaginal bleeding and a positive urine pregnancy test. She noted that this was a strongly desired pregnancy. She had surgical intervention in the past for an ectopic pregnancy: she was certain she had not had a salpingectomy. She had minimal abdominal pain. Vital signs were normal and she had a benign abdominal examination. [did you do a pelvic exam?] Pertinent laboratory findings included a normal hemoglobin of 12.5 g/dl and a beta HCG of 1150 IU/L. "

97-103. "The patient was counseled about the findings, and urgent surgical management was recommended. She expressed a strong desire to maximize future fertility and the surgical plan was to try to preserve the affected tube if possible".

107. How much blood? Given that you chose to do the chromeopertubation, it must not have been much or you would have controlled the bleeding somehow. Please comment.

109. I'm a bit unclear why you needed to prove that the tube was absent. Were there intraoperative findings that made this obscure somehow?

110. Could you comment on the status of the left tube since that was the purpose of the chromopertubation?

115. How long did you observe the right tube before deciding she was stable?

Discussion: please include the recurrence rate of ectopic pregnancies in your discussion.

Discussion: Please avoid repeating a lot of information from the introduction

Perhaps Lines 122-159: could be condensed to “All current surgical approaches to treat ectopic pregnancy can result in either absence of the tube or a risk of tubal scarring or injury. [Then please provide some data from the literature on risks of infertility or recurrent ectopic in women with prior ectopic in general, and with salpingectomy, salpingostomy, salpingotomy. Its not necessary to describe the surgeries themselves]

In our patient, we elected to perform chromopertubation to be certain of the status of the patient’s contralateral fallopian tube before proceding with surgical management of her ectopic. The incidental finding that an intact ectopic pregnancy was extruded from the tube suggests that this may be a potential approach to treatment of an unruptured bleeding tubal ectopic. [you wouldn’t suggest this for a ruptured ectopic would you? This patient clearly had a tubal abortion and hemoperitoneum from that, not a ruptured ectopic, don’t you think?]

This approach has the potential to eliminate iatrogenic tubal injury from surgery. Even so, many questions remain and should be considered in planning follow up for these patients and future potential research. We suggest that potential candidates are women who desire future fertility and whose affected fallopian tube appears intact at the time of surgery. Women who are unstable or actively and heavily bleeding should have rapid and definitive treatment offered. Future pregnancy outcomes compared to tubal surgical treatment should be assessed. As prior tubal infection is a risk factor for ectopic pregnancy, there is a hypothetical concern that chromotubation could cause efflux of microorganisms into the peritoneal cavity and as such, monitoring for post operative infection is warranted.

Although many questions remain, this case suggests the possibility that in selected cases, chromopertubation under laparoscopic control may successfully dislodge an ectopic pregnancy from a fallopian tube, avoiding tubal surgery and potentially decreasing future infertility issues.”

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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). 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. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Case Reports should not exceed 8 typed, double-spaced pages (2,000 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.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A

Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

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 40 characters, including spaces, for use as a running foot.

8. 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."

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

In addition, the abstract length should follow journal guidelines. The word limit for Case Reports is 125 words. Please provide a word count.

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

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

12. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

13. 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%").

14. 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

15. Figures 1 and 2 may be resubmitted as-is with your revision.

16. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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 30 days from the date of this letter. If we have not heard from you by Sep 16, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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

September 28, 2020

Editor

Obstetrics & Gynecology

RE: Manuscript ID ONG-20-2095

Dear Editor,

We would like to thank you and the Reviewers for the thoughtful comments provided. We also truly appreciate the opportunity to revise our Case Report and the additional time for edits. We believe that the suggestions we have been given have made our manuscript more focused and impactful. We will address each comment individually. We have attached a manuscript version with the Track Changes as well as a "clean version" with the Track Changes accepted for ease of readability. The line numbers refer to the revised Track Changes version. Each author has approved the final form of the revision. Regarding the inquiry of transparency around peer-review, we opt-in to publication of our point-by-point response letter. This letter serves as confirmation we have read the Instructions for Authors for this article type (i.e. Case Report). The patient provided written informed consent for publication of this report.

Best regards,

Sowmya Sunkara, MD

REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review this manuscript. This is an interesting case report and it is well written. The authors of this manuscript described a case of ectopic pregnancy which chromopertubation was used resulting in expulsion of tubal pregnancy. This is a challenging clinical scenario as the patient desired to preserve future fertility. Often times, patients in similar scenario are counseled about the need to remove of the effected tube and they may have to pursue IUI as an alternative for future pregnancy. The dilemma is that patient may come back with another ectopic pregnancy and need for an additional surgery.

Here are my comments and questions:

1) The incidence of ectopic pregnancy increases three to eight folds in patients who had prior ectopic pregnancy. As it is mentioned in this case she had one prior ectopic pregnancy and salpingectomy in the contralateral tube. Do you have more information regarding patient's past history such as STI, endometriosis and any other pelvic surgery? I think it is important to describe clinical presentation in details

We thank the Reviewer for this suggestion. The patient had no history of STIs, endometriosis, or other pelvic surgeries. This information was added in lines 218 to 219.

2) Line 54, 55: You mentioned " Chromopertubation…. an alternative treatment to surgical removal of

the tube or damaging fallopian tube". She had patent fallopian tube in the OR, Did you consider HSG 3 months postoperatively to confirm tubal patency? My concern is the underlying pathology she may have had resulting in two ectopic pregnancies. It is also hard to exclude the tube is intact even after expulsion of ectopic pregnancy and there is no residual damage as there is no data to support this claim.

We agree with the Reviewer and have similar concerns. Our plan was to perform an HSG 3 months postoperatively to confirm tubal patency. Unfortunately, the patient was lost to follow up. We agree that follow up to assess for future fertility and potential complications should be performed and this was added as a teaching point in line 111-112 and to lines 407-408 in the case portion

3) Line 91, What was the patient's Hematocrit? The clinical presentation described a stable patient with no major drop in her Hemoglobin and normal vital signs. The ultrasound finding appeared as a ruptured pregnancy! Did you consider observation and serial H&H given the fact that patient strongly desired future fertility?

The hemoglobin was added to line 221. The patient was counseled on the clinical findings; however, in the setting of a high suspicion for tubal rupture, surgery was recommended. While the patient was clinically stable at presentation, in the setting of a suspected ruptured ectopic pregnancy the physician staff did not feel comfortable offering expectant management. Further, rapid surgical intervention (while the patient was hemodynamically stable) was believed to provide an option of conservative surgical intervention (i.e. salpingostomy versus salpingectomy).

4) Please describe the location of ectopic pregnancy in the tube.

Thank you for this suggestion. This information has been added to line 232

5) Did you go to the OR with the intention of using chromopertubation in for expulsion of this ectopic or to ensure the presence of left tube? Please clarify in your manuscript.

Thank you for noting this. We have clarified why the chromopertubation was performed and this has been added to lines 392 to 394.

6) Lines 156, 157: Please describe the multiple factors that need to be taken into account regarding management options.

We have removed this line. We have added to lines 504 to 506 to describe the clinical situations in which this management may be an option and those in which it should not be.

7) I suggest labeling your figures as it helps the reader to orient and better appreciate the location of the pregnancy in the tube.

Thank you for the suggestion, we have added labels to the figures.

Reviewer #2: Thank you for the opportunity to review your work. As a MIGS surgeon, I was really excited to read this report! To the best of my knowledge, I could not find any case reports or descriptions of

such technique. Pure genius!

I have some questions and comments below

1. Images and video

a. Do you have any other photos aside from what you have? They are quite limited-before and after pic, but none showing how it was done (i.e. no in-between). Do you have those "in-between" pics? If yes, please add.

We are happy to add additional ultrasound pictures and intraoperative photographs. Unfortunately, we do not have a video to provide. However, we were not sure how much clinical information it would add to the report to add the ultrasound and additional intra-operative photographs. However, if the journal prefers, we can add these photos as supplemental digital material. Please just let us know how the journal wishes to proceed.

b. Video-for a novel technique like this a video would be a make or break it, and it would have all the details of how you did it so that others could watch for details in order to replicate it. Do you have a video? If yes, please add.

Unfortunately, we did not record this surgery (our loss).

2. Related surgical technique

a. Please add reference below to your text. Although they use vasopressin injection instead of chromotubation it is same idea.

https://urldefense.proofpoint.com/v2/url?u=https-3A__surgeryu.com_detail_1045&d=DwIGaQ&c=ZQs-KZ8oxEw0p81sqgiaRA&r=qwTY2u2huv5tq2pZSvt3sd_eOD6dGqcu19RxtCRrgtk&m=oQiQE_I_X4NcXNLOPq11zmmZspfayCJ3KroaTDxlE9I&s=aQd2CBOK5qPgK3ZMjHesn2usLIlboxNDJ8g8qj5Y6yA&e=
Tubal Flushing A Novel Treatment Modality for Ectopic Pregnancy
Jayakrishnan K Krishna Pillai,MDDivya S Nambiar,MD

Thank you for bringing this video to our attention, it is very interesting. Unfortunately, the Green Journal does not allow the use of video abstracts presented at meetings as references.

b. Please comment why you did not inject vasopressin into the tube first

a. That would help you with hemostasis in case it bleeds from ectopic site

The method we used to expel the ectopic pregnancy from the fallopian tube was not planned and, thus, we had no indication to inject vasopressin into the fallopian tube.

b. How would you address bleeding if it did not stop after flushing?

i. Maybe inject topical fibrin agents into the tube?

Typically would use standard surgical techniques to manage ongoing bleeding from the fallopian tube. These could include the use of cautery, removal of the fallopian tube, and potentially the use of topical fibrin agents. Since this did not occur in the case (fortunately) we did not comment on this aspect.

ii. Other thoughts?

c. Tubal flushing

a. As been studied for subfertility, please add to your discussion/intro as it seems to be relevant

Thank you for the suggestion, we do not feel this topic is within the scope of our discussion since these techniques are not utilized in the context of an ectopic pregnancy.

b. Consider putting "tubal flushing via chromotubation" into your title as that might make it clearer

Thank you for the suggestion; however, since this occurred serendipitously after a chromopertubation and not a planned “tubal flushing” we did not believe this should be in the title.

d. Tubal milking

This technique has been described in conservative management of ectopics. Please add references and incorporate into intro/discussion.

Thank you for this suggestion. We have a description of this technique on lines 496 to 498 with a citation.

3. How did you think of this technique? What made you think it was feasible? Please explain how you came up with this idea

Our initial intent was to evaluate the patency of the left fallopian tube to counsel the patient postoperatively (we have added this description on lines 392 to 394). When we visualized the right ectopic pregnancy moving to the distal portion of the fallopian tube at the time of chromopertubation, we felt that continued installation of fluid through the cervix, into the uterine cavity may cause the ectopic to expulse entirely from the fallopian tube. Given that the tube was unruptured and the patient was stable, we felt that an attempt to do this would not increase the risk of morbidity to the patient. This process is described in line 394 to 402.

4. Tubal flushing w/chromotubation vs. salpingostomy. How did you make this decision intraop?

See above

5. Teaching points need to be revised.

a. 1st teaching point is too strongly worded-this is only proof of concept and you can't say anything about damage or fertility outcomes at this point

Thank you for pointing this out. We have concluded that since this was not a teaching point of this case we have removed this.

b. 2nd point is a bit off. Would it be better to say that it might be alternative other tube-sparing techniques?

Thank you, the teaching points has been revised accordingly.

6. Case details

a. Was there an signs intraop that ectopic was aborting? Description on line 107 sounds like aborting ectopic.

While the ectopic pregnancy was in the distal portion of the fallopian tube, we are unable to know definitively if it was in the process of spontaneously aborting, however it is suggested so this was indicated in line 391

b. Lines 58-73 need to be re-written to take focus off ectopic reviews and to focus on existing tube sparing options.

Thank you for this suggestion. We have edited the beginning of the introduction to make it more focused and succinct.

c. Edit entire report for style, spelling and grammar.

i. Ex line 79. "gravida three, para 1" is odd. "gravida 3, para 1"?
ii. Ex. line 77 "therefore"

We have taken this recommendation and have thoroughly edited the report.

d. Line 77. Did you obtain consent from patient for publication of this report and for use of images?

Yes, we added this information in lines 212 to 213.

e. Lines 79-89 can be condensed, and redundancies removed to retain the following facts
i. Pt strongly desired childbearing
ii. She was not able to afford ART and having her tubes was he only hope
iii. She was willing to accept higher risk of recurrent ectopic with tubal conservation and need to follow betas serially with potentially needing MTX for retained POCs
iv. She did not have her op reports and recalled that she had salpingostomy on one side but did not know which.
v. Patient had eval at outside clinic but did not have records and entire eval was reported in the ED.

Thank you, we have edited the case description significantly to make it more focused and succinct.

f. Lines 105. Please describe
i. exact location in the tube (which portion-ampulla?)

This was added to line 232

ii. size in cm of ectopic

This was added to line 406

iii. presence or absence of tubal damage

This has been added in line 390

iv. Why did you use Kahn canula instead of a Humi? The latter could theoretically generate more pressure.

We practice at a safety net hospital and the Kahn canula is the standard part of the laparoscopic instrument set that is available at our institution for laparoscopic cases. While we agree with the Reviewer, this was what we had initially begun the case with. In addition, since we did not anticipate our findings, we did not consider the aspect of intra-tubal pressure generation. With a future procedure this may be considered.

7. Lines 126-130. Other techniques involve use of vasopressin, microelectosurgery, and topical fibrin products (floseal) to achieve hemostasis

In order to focus our report and make it more succinct, we have removed the description of commonly utilized surgical techniques used to manage ectopic pregnancies.

8. Consent. Given that you decided to utilize this novel technique, how did you counsel pt. on this preop?

The patient made her wishes regarding preservation of fertility known to us prior to the surgery. We counseled the patient regarding all standard management options for ectopic pregnancy. Since the patient was unclear what prior surgery she had on her contralateral tube, we explained that it would be assessed.

9. Lines 146-148. Given that this is only report describing this, I would re-write that you need to consider safety issues and candidate selection I future work, but not state your ideas as recs.

Thank you. We have revised the discussion to reflect this.

10. Line 157. What are "special populations" are you referring to? Those who cannot afford IVF? That gets to reproductive justice issues…

We have added a description of patients that may be candidates for this type of management to the Discussion section.

11. What would be next steps in studying this further?

Next steps would include assessment of future pregnancy outcomes using this technique versus other surgical techniques, and assessment of tubal patency at least 3 months after this procedure is performed. We have added this information to the Discussion section.

Reviewer #3: The article is a case report of surgical technique involving chromopertubation to expel a tubal ectopic pregnancy. It is a fascinating idea and I feel (following substantial revision) this article can change management of certain patients.

Thank you, we agree and have made substantial revisions as suggested.

I have multiple questions/comments regarding the manuscript (the first number is a line to which the comment is most appropriate). I also suggest an English language editor to review the article.

58 - cervical pregnancy is also considered ectopic, please modify definition (e.g. outside of normal location of endometrial cavity)

Thank you, this has been clarified in lines 117 to 118

59 - please mention that treatment option depends on location

Thank you, this has been added in line 119

62 - instability - replace

We have clarified this as “hemodynamic instability” on line 121

64-65 - laparotomy as a method of choice is relatively remote history

We agree, and this information does not feel relevant to our report and we have removed it.

67 - salpingostomy vs salpingotomy - I am not clear on the difference, the reference you providing (ACOG PB #193) doesnt' distinguish these procedures.

We have add a description on lines 125 to 127

In general in introduction section I would suggest to add a brief overview of comparative fertility outcomes among patients undergoing various treatment options of tubal ectopic (MTX, salpingostomy, salpingectomy). I would also suggest reviewing the concern of prior tubal damage as a main risk factor for ectopic pregnancy.

Thank you for this suggestion, we have included this overview in the introduction.

74 - please briefly describe chromopertubation in introduction section

We believe that Obstetrician/Gynecologists understand this technique since it is part of their training, so therefore we did not add an explicit definition. However, if the editorial board considers this necessary, we are glad to add this.

81 - invention?

Thank you for catching this error. We meant intervention, and have corrected this in line 184

85-87 - I am not sure description of positive pregnancy test result and absent records of current pregnancy are clinically relevant in this case

Agree. We have edited the case report to include only the most relevant information.

91 - it would be nice, but not necessary to have sonographic images

Thank you for the suggestion, while we not opposed to this we were not sure how much information this would add for readers. If the journal believes this is of benefit, we can add some pictures in the Supplmental Digital content.

108 - I am not aware of the verb "chromopertubate" - perform chromopertubation

Thank you for catching this. This has been corrected throughout the document.

109-114 - I admire your honest description of the technique - it seemed you basically stumbled upon it by accident - this is just great.

Thank you. As the quote by Horace Walpole states, “a knack for discovery involves a combination of accident and wisdom while pursuing something else.”

Discussion - again, your main point seems to be preservation of fertility, therefore I would recommend stressing that aspect in your discussion rather than description of salpingectomy/salpingostomy which you did not (fortunately) perform in this case.

Agree, we have removed these descriptions to make the Discussion more focused on this aspect.

In my personal experience doing chromopertubation during surgery for EP is somewhat difficult - probably due to tubal or endometrial edema. Can you please address that? Are there any studies of chromopertubation during surgeries for ectopic (after salpingectomy)?

We were unable to find any studies regarding the use of chromopertubation during surgeries for ectopic pregnancies. Your point is well taken, but fortunately, this was not our experience in this case.

The article by Decherney is from 1985 - are there any more recent references on the subject?

The part of the Discussion that referenced this article has been removed in attempt to make the report more focused and succinct.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

We have carefully reviewed the instructions for authors and have gone through the report, keeping those instructions in mind. Major revisions with corrections have been made to comply

Numbers below refer to line numbers.

I'm going to be making some substantial recommendations to make your paper more succinct and focused. Please make sure that my suggestions reflect the truth and emphasis you wish to express.

43. "tubal damage" seems a bit oblique to me. I believe what you are referencing here is salpingostomy with risks of tubal scarring. Would you consider saying here, and elsewhere that you use "tubal damage" ".."either salpingectomy or salpingostomy with risk of tubal injury"?
Thank you for this suggestion, we have removed the phrase "tubal damage" from the report and instead refer to "risk of tubal injury."

44. Rather than say "the following case", consider something like "A patient with a prior ectopic pregnancy in the left tube presented with an ectopic in the right one. As the patient strongly desired future fertility and the intraoperative status of the right tube could not be confirmed, chromopertubation was performed and incidentally, the ectopic pregnancy was expelled from the right tube".

This is a little clearer and is an important focus for your revision. As the full paper is written, it is clear that you did not perform the chromopertubation for the purpose of flushing the tube w/ the ectopic. This was all incidental or serendipitous and needs to be presented as such throughout.
We agree and have edited this portion of the manuscript to improve the language per your suggestion above. We have also made edits to ensure that it is clear that it was not our initial surgical plan to flush the ectopic pregnancy out of the fallopian tube and that we only decided to attempt this upon seeing how the chromopertubation moved the ectopic towards the distal portion of the tube.

52. Even in patients who don't strongly desire future fertility, these surgeries can cause damage or impair fertility. Perhaps " Salpingectomy and salpingostomy done for surgical management of ectopic pregnancy may impair future fertility".
Thank you. After further reflection we have opted to delete this teaching point since this was not an aspect of this case and was more of a statement suggested by the medical literature. If you feel we should include this point we will make this edit.

54. Perhaps "Chromopertubation of an unruptured ectopic pregnancy under laparoscopic visualization may be an alternative to salpingectomy or salpingostomy".
Thank you, this edit was made to Teaching Point 1 in line 81

I do think its important to add the information that this was not done blindly. You are proposing an interesting alternative. Most people will only read the abstract and teaching ponts so this needs to be clear. Third teaching point would be "Follow up patients treated with chromopertubation is important to assess for future fertility and potential complications of this treatment".
Yes, we agree and we have added this Teaching Point 2 in line 83

Please number the 2 teaching points.
We have made this change

58: perhaps “Approximately 2% of pregnancies in the United States are ectopic, with implantation outside of the uterus and most commonly in the fallopian tube” is better?
Yes, this language is better and we have edited line 117-118 of the Introduction per your suggestion.

63. Aren’t there also contraindications such as size of the ectopic, presence of a fetal heart beat?
Yes, thank you for pointing this out. These edits have been added in lines 122 to 125.

64. Delete lines 64-66. You can just say “Surgical management includes laparoscopic salpingostomy, salpingotomy or salpingectomy. While surgically successful for treatment of the ectopic pregnancy, these approaches can result in impaired fertility and tubal scarring. As such, with a recurrent ectopic in the contralateral tube, surgical planning must be tailored to incorporate the patient’s desire for future fertility”
We have edited this portion of the introduction to be more in line with the above language.

Please also add a reference for the actual data (which should be included) o
This data was added to the report in lines 131 to 135 and has been referenced.

74. “The case to follow describes a potential alternative approach to remove a tubal ectopic pregnancy without surgical intervention of the fallopian tube. “ Delete sentence starting w/ “IRB approval…”.
This sentence has been deleted.

79-91: this can be made much more succinct: “The patient is a 35 year old, G3 P1011 seen in the emergency room for vaginal bleeding and a positive urine pregnancy test. She noted that this was a strongly desired pregnancy. She had surgical intervention in the past for an ectopic pregnancy: she was certain she had not had a salpingectomy. She had minimal abdominal pain. Vital signs were normal and she had a benign abdominal examination. [did you do a pelvic exam?] Pertinent laboratory findings included a normal hemoglobin of 12.5 g/dl and a beta HCG of 1150 IU/L. “
Thank you, we have revised this portion of the Case description to be more succinct per your above recommendation.

97-103. “The patient was counseled about the findings, and urgent surgical management was recommended. She expressed a strong desire to maximize future fertility and the surgical plan was to try to preserve the affected tube if possible”.
We have edited this portion, per your suggestion on lines 200 to 202

107. How much blood? Given that you chose to do the chromeopertubation, it must not have been

much or you would have controlled the bleeding somehow. Please comment.
Yes, thank you for this suggestion. We added this information to line 356

109. I'm a bit unclear why you needed to prove that the tube was absent. Were there intraoperative findings that made this obscure somehow?
The patient expressed that she did not know the specifics about the surgery that was performed for her previous ectopic pregnancy, but she was sure that there was not removal of a fallopian tube during that surgery. Given her strong desire for future fertility if we had to remove her remaining fallopian tube, we felt it was better to demonstrate definitely that there was no intact tube on the left. We felt this would allow the patient to have certainty regarding this and aid us in postoperative counseling. We have clarified this in line 358 to 360.

110. Could you comment on the status of the left tube since that was the purpose of the chromopertubation?
We have added this information to lines 361 to 362.

115. How long did you observe the right tube before deciding she was stable?
The tube was observed for several minutes and a low-pressure check was performed to ensure hemostasis. We have described this in lines 367 to 368.

Discussion: please include the recurrence rate of ectopic pregnancies in your discussion.
Thank you for this suggestion. We have added a paragraph to the introduction that details recurrence rates of ectopic pregnancies based on various management options. We have also included the reference for this data.

Discussion: Please avoid repeating a lot of information from the introduction
Thank you for noting this. We have substantively edited the Discussion to remove extraneous and repetitive information.

Perhaps Lines 122-159: could be condensed to "All current surgical approaches to treat ectopic pregnancy can result in either absence of the tube or a risk of tubal scarring or injury. [Then please provide some data from the literature on risks of infertility or recurrent ectopic in women with prior ectopic in general, and with salpingectomy, salpingostomy, salpingotomy. Its not necessary to describe the surgeries themselves]
Thank you for this suggestion, it does a better job of conveying our point. We have added data regarding fertility rates and ectopic recurrence rates based on type of management to the Introduction. We have removed the lengthy descriptions of standard surgical techniques.

In our patient, we elected to perform chromopertubation to be certain of the status of the patient's contralateral fallopian tube before proceding with surgical management of her ectopic. The incidental

finding that an intact ectopic pregnancy was extruded from the tube suggests that this may be a potential approach to treatment of an unruptured bleeding tubal ectopic. [you wouldn't suggest this for a ruptured ectopic would you? This patient clearly had a tubal abortion and hemoperitoneum from that, not a ruptured ectopic, don't you think?]
Yes, we agree. We have clarified this in lines 464 to 468 and edited the language per your suggestion.

This approach has the potential to eliminate iatrogenic tubal injury from surgery. Even so, many questions remain and should be considered in planning follow up for these patients and future potential research. We suggest that potential candidates are women who desire future fertility and whose affected fallopian tube appears intact at the time of surgery. Women who are unstable or actively and heavily bleeding should have rapid and definitive treatment offered. Future pregnancy outcomes compared to tubal surgical treatment should be assessed. As prior tubal infection is a risk factor for ectopic pregnancy, there is a hypothetical concern that chromotubation could cause efflux of microorganisms into the peritoneal cavity and as such, monitoring for post operative infection is warranted.

Although many questions remain, this case suggests the possibility that in selected cases, chromopertubation under laparoscopic control may successfully dislodge an ectopic pregnancy from a fallopian tube, avoiding tubal surgery and potentially decreasing future infertility issues."
Thank you for these edits. We have incorporated them into our Discussion section and, as a result, we feel that this section is more focused and impactful.

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:

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7. Provide a short title of no more than 40 characters, including spaces, for use as a running foot.
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We have standardized our presentation of data throughout the report

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