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.
RE: Manuscript Number ONG-20-3053

Buprenorphine patch as a bridge to sublingual treatment of opioid use disorder in pregnancy

Dear Dr. Galati:

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 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The authors report the results of a small observational study describing the innovative use of buprenorphine patches as an assist to the induction of sublingual buprenorphine. They propose that a substantial benefit of this approach is that it avoids excessive withdrawal symptoms often associated with induction with sublingual patches alone. Of course, this leads to subsequent failures with buprenorphine.

This report is appropriate for a brief report in letter form. The report may be a first step in using this technique in a larger and more systematic study. Because it is brief, the table showing individual outcomes is helpful. The induction protocol described in a flow chart may be useful for further investigation. It should be emphasized that the authors have reported this approach in a controlled and regulated manner in a letter report format. Further investigation may verify the value of this patch to sublingual approach.

Reviewer #2:

The authors describe "successful" buprenorphine induction in 8 pregnant women via use of a transdermal patch to bridge to sublingual therapy. These findings are particularly notable because a majority of these women had previously failed prior attempts at buprenorphine induction due to inability tolerate withdrawal symptoms.

While I certainly appreciate that the authors are trying to explore alternative treatment options for women with severe OUD, I cannot agree that the data presented is sufficiently supportive of their claims. Of primary concern, all of the women who did outpatient induction therapy and presented for follow-up were positive for illicit opioids (and one didn't even have buprenorphine metabolites in her urine). Although none of outpatient initiation group reported withdrawal symptoms with induction/bridge therapy, all of those who followed up were still using illicit narcotics. It is, therefore, impossible to say that induction therapy was effective in this group. In the inpatient initiation group, 3 out of 4 were hospitalized for labor. Although they reported either no or mild withdrawal symptoms only, it seems entirely plausible that other factors leading to symptom mitigation may have been at play (supportive medications, concurrent narcotics administered for lacerations/cesarean/PP pain, additional support from hospital personnel, etc). Although it is encouraging that all the women who initiated in an inpatient setting were still clean during their follow up visit, this may have been due to ulterior motivations (2 had new babies, one had been very ill with endocarditis/heart failure).
Based on the array of cofounding variables and patient heterogeneity in this study cohort, I think it would be premature to conclude that bridge therapy with buprenorphine patch represents an "effective" induction therapy, at least based on the data presented in this research letter.

Specific Comments:
* Introduction, line 8: Is it really true that in large part women with OUD don't receive buprenorphine because of initiation challenges? If so, can a reference be provided?
* Should the GA be presented as a median rather than a mean? Doesn't seem like it's normally distributed.
* Can you further explain/characterize the prior failure attempts reference in results (line 4)? Were there all attempted as an outpatient? How far did they make it in the induction process?
* Interesting that all the patients were using fentanyl with no heroin users in the group. Could that affect the successful/failure of buprenorphine induction in general? Is this population somehow unique compared to other women with OUD?
* Results, line 7: "successful" is a tricky word here...seems like it depends on how success is defined. I'd consider removing or rewording.
* Discussion, line 4: I'm not sure how "unachievable" this would have been previously if women had continued using illicit opioids, which is the situation described for about half the study participants.

Table comments:
- It would be useful to know how long women were admitted in the inpatient induction group.
- There is no mention of the daily phone calls and how many resulted in successful contact. Was this tracked?
- Patient #2 should not have been included, correct? Since she had a COWs score >6?

Reviewer #3:
Comments to the author:

The authors present a timely research letter on the use of buprenorphine patch as a bridge to sublingual treatment for opioid use disorder in pregnancy. Although only a small case series, this letter addresses a serious issue with a less frequently discussed problem of induction. Any small improvement may pave the way for larger trials.

Introduction:

This is a good review of the challenges and pathophysiology of the induction process.

Line 53 In review of the citation Drug Alcohol Depend. 106 2018; 192:146-149. DOI: 10.1016/j.drugalcdep.2018.07.042 they list 64% adhere. I would recommend adding this type of quantitative background to put the challenge into context and contrast to your study.

Methods:

Line 63 Although retrospective this seems to be a descriptive case series. Were these patients previously failed induction on sublingual treatment? If not, a matched control group would be an interesting comparison, but the power may be too small for meaningful outcomes.

Results:

Line 73-74 Are there differences in success for treatment and induction with fentanyl vs other opioids like oxycodone or heroin? It looks like all included patients were fentanyl only. Was there other confounder or challenges with polysubstance use as well?

Table 1 I would recommend explaining the use of COWS scoring system and how it is used. It may not be familiar to all the readers.
Were there results for neonatal outcomes?

Discussion:

Concise with clinical relevance.

STATISTICS EDITOR COMMENTS:

lines 24-25: A sample of n = 8 seems too few to generalize re: effectiveness of this method, especially since (lines 83-84) 1/2 of the patients in this series were still using illicit opioids, despite the patch, which may have contributed to the no or mild withdrawal symptoms (lines 75-76). In other words, need more measured, less conclusive statements re: effectiveness and amelioration of withdrawal symptoms based on this small sample.

lines 72-73: With a sample size of only n = 8, estimation of SD is imprecise, Should simply state the mean or median with ranges for the maternal and gestational ages.

EDITOR COMMENT:
1. Thank you for submitting this work to Obstetrics and Gynecology. In your revision, it will be particularly important to address the comments from the statistical editor regarding toning down all statements related to demonstrating efficacy. As such, the Precis will need to be modified as well.
2. Given that this is a case series of 8 patients, adding a control group would not allow for any definitive statements. Therefore, it is fine to just submit the revision as a case series (rather than adding a control group as requested by one of the reviewers).

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. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and
ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting observational studies (ie, STROBE). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. 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.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Research Letters articles should not exceed 2.5 pages (600 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.

7. 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).

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.
9. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

10. 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.

11. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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).

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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. Do not omit your responses to the Editorial Office or Editors’ comments.

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 28, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri Metz, MD
Associate Editor, Obstetrics

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
Dear Editors of *Obstetrics & Gynecology*,

We thank you for the opportunity to revise our research letter for *Obstetrics & Gynecology*. We believe the revisions have resulted in a significantly improved manuscript. Please find our reviewer replies and revisions.

**Author declaration of transparency**

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Signed by:  

*The manuscript’s guarantor

This research was considered exempt by the Washington University Institutional Review Board.

Sincerely,

Bridget Galati, DO; corresponding author

Washington University School of Medicine, Department of Psychiatry
Of note, we have obtained follow up data from patient number 8 and our results and tables have been updated with this information.

REVIEWER COMMENTS:

Reviewer #1:

The authors report the results of a small observational study describing the innovative use of buprenorphine patches as an assist to the induction of sublingual buprenorphine. They propose that a substantial benefit of this approach is that it avoids excessive withdrawal symptoms often associated with induction with sublingual patches alone. Of course, this leads to subsequent failures with buprenorphine.

This report is appropriate for a brief report in letter form. The report may be a first step in using this technique in a larger and more systematic study. Because it is brief, the table showing individual outcomes is helpful. The induction protocol described in a flow chart may be useful for further investigation. It should be emphasized that the authors have reported this approach in a controlled and regulated manner in a letter report format. Further investigation may verify the value of this patch to sublingual approach.

Response: We thank you for these helpful suggestions. Our brief letter format limits us to 2 tables, and thus our protocol was organized as Table 1. We are happy to revise Table 1 into a flowchart diagram with permission from the editors if preferred.
Reviewer #2:

The authors describe "successful" buprenorphine induction in 8 pregnant women via use of a transdermal patch to bridge to sublingual therapy. These findings are particularly notable because a majority of these women had previously failed prior attempts at buprenorphine induction due to inability to tolerate withdrawal symptoms.

While I certainly appreciate that the authors are trying to explore alternative treatment options for women with severe OUD, I cannot agree that the data presented is sufficiently supportive of their claims. Of primary concern, all of the women who did outpatient induction therapy and presented for follow-up were positive for illicit opioids (and one didn't even have buprenorphine metabolites in her urine). Although none of outpatient initiation group reported withdrawal symptoms with induction/bridge therapy, all of those who followed up were still using illicit narcotics. It is, therefore, impossible to say that induction therapy was effective in this group. In the inpatient initiation group, 3 out of 4 were hospitalized for labor. Although they reported either no or mild withdrawal symptoms only, it seems entirely plausible that other factors leading to symptom mitigation may have been at play (supportive medications, concurrent narcotics administered for lacerations/cesarean/PP pain, additional support from hospital personnel, etc.). Although it is encouraging that all the women who initiated in an inpatient setting were still clean during their follow up visit, this may have been due to ulterior motivations (2 had new babies, one had
been very ill with endocarditis/heart failure).

Based on the array of cofounding variables and patient heterogeneity in this study cohort, I think it would be premature to conclude that bridge therapy with buprenorphine patch represents an "effective" induction therapy, at least based on the data presented in this research letter.

Response: We thank you for these thoughtful and helpful suggestions and comments.

1. We agree that the on-going illicit opioid use in a majority of patients at follow-up is an important point. But, our sole focus here is the success of buprenorphine induction, which is measured by the ability of a patient to start and tolerate regular sublingual doses of buprenorphine for OUD treatment. Successful induction necessitates that the majority of μ-receptors are engaged and blocked by buprenorphine so that subsequent sublingual doses do not precipitate withdrawal, and is the first major initial step toward OUD treatment. Because of this blockade, overdose risk (and euphoria) is decreased even with concurrent opioid use. Ongoing opioid use concurrently with buprenorphine (or methadone) treatment is a frequent occurrence in patients with OUD that typically decreases over time as patients engage further in recovery services,¹ and is referred to in the literature as “OUD recovery.”

We specifically limited the scope of this manuscript solely to the induction process.

1. Bell, J, Strang J. Medication treatment of opioid use disorder. Biological Psychiatry; 87, 1, 2020; 82-88. DOI: 10.1016/j.biopsych.2019.06.020

We have revised the following lines to better reflect our limited scope that focuses solely on buprenorphine induction success:
“The majority presented to their 1-week follow-up appointment (7/8), with completed induction onto maintenance sublingual buprenorphine doses confirmed by urine metabolites (6/7), although half of patients still had illicit opioids concurrently confirmed as well (4/7).”

We are happy to incorporate further explanation of buprenorphine induction and into our letter in the introduction, with permission from the editors given the current character constraints of this research letter:

Line 57:
Successful buprenorphine induction is measured by the ability of a patient to start and tolerate regular sublingual doses of buprenorphine without precipitating withdrawal, and necessitates that the majority of µ-receptors are engaged and blocked by buprenorphine so that subsequent sublingual doses do not precipitate withdrawal. An alternative induction method initiates buprenorphine in microdoses, administered via a transdermal patch, as a bridge to sublingual buprenorphine....

2. We agree that obstetric patients have “ulterior motives” to engage in recovery services either during prenatal care or postpartum, which is what makes treating OUD in this population so rewarding! We think our numbers here are too small to make any strong comparisons between inpatient and outpatient settings, but rather, suggest a promising
alternative method of buprenorphine induction in both settings. We agree that we should not use “effective” to describe this method based on our results and have removed this word from the precis to reflect this excellent point:

“The buprenorphine transdermal patch can be used as a method of induction in pregnant patients with active opioid use disorder.”

Specific Comments:
* Introduction, line 8: Is it really true that in large part women with OUD don’t receive buprenorphine because of initiation challenges? If so, can a reference be provided?

Response:
Unfortunately, buprenorphine initiation is a major challenge in OUD treatment (both in and out of pregnancy). This is due to 2 reasons:

1. **Providers** don’t have infrastructure or experience. Buprenorphine induction is traditionally done in a planned office visit so that the first sublingual doses can be given under observation, to avoid the potential of precipitated withdrawal. However, this approach requires dedicated staff, office space, and planned logistics of a second visit specifically for induction, and these are the most commonly cited barriers to providing buprenorphine treatment.1-3 Alternatively, patients can undergo unobserved home induction, in which they are sent home with a supply of buprenorphine, instructions on use, and clinician phone support. This method of buprenorphine induction is routinely used successfully as standard of care in the non-pregnant population to decrease the
burden on both patients and providers,\textsuperscript{1-3} but currently no data exists for this method during pregnancy.

2. \textit{Patients} often cite withdrawal symptoms during induction for the reasons behind buprenorphine treatment dropout. This is well known in the non-pregnant literature.\textsuperscript{5} Buprenorphine induction during pregnancy, however, is not studied well. The largest trial using buprenorphine during pregnancy, the Maternal Opioid Treatment: Human Experimental Research (MOTHER) trial, required \textit{inpatient admission} for initiation of treatment. Despite this, more women assigned to the buprenorphine group dropped out compared to those assigned to methadone, and the majority of those women withdrew during the initial induction phase, with significantly sharper initial increases in withdrawal scores.\textsuperscript{4} Additional research has shown that pregnant women with higher opioid withdrawal symptoms were less likely to be adherent to treatment.\textsuperscript{6}

The above two points unfortunately cannot be fully explored in our letter due to word count restraints, but we briefly address them in lines 53-55. The patch is an attractive alternative method because it addresses \textit{both} of these barriers for induction: providers do not need to have infrastructure for multiple visits, and patients do not need to experience moderate or severe withdrawal symptoms.

References:


* Should the GA be presented as a median rather than a mean? Doesn't seem like it's normally distributed.

**Response:** We agree and have presented GA as median age.
Can you further explain/characterize the prior failure attempts reference in results (line 4)? Were there all attempted as an outpatient? How far did they make it in the induction process?

**Response:** Yes, all prior attempts at sublingual induction were attempted as outpatient, and the patients were not able to either present for their scheduled induction, or returned without being able to start buprenorphine at home. For patients with severe disease, this is unfortunately a frequent occurrence in OUD treatment, as they are unable to tolerate or achieve the withdrawal necessary to induce buprenorphine. We are unable to offer inpatient admission *solely* for buprenorphine induction/OUD treatment as we are not a federally licensed Opioid Treatment Center, much like the vast majority of tertiary care centers. We did not further characterize these attempts in the manuscript due to limited word count.

Interesting that all the patients were using fentanyl with no heroin users in the group. Could that affect the successful/failure of buprenorphine induction in general? Is this population somehow unique compared to other women with OUD?

**Response:** Fentanyl is 50 to 100 times more potent than morphine, and given its potency, it could prove more difficult for individuals dependent on fentanyl than heroin to transition to medication assisted therapy. However, no studies exist to compare the two. Our current local illicit opioid supply is heavily skewed toward fentanyl over heroin, and the authors (who staff
our opioid-specific prenatal and postnatal clinics) actually cannot recall any urine drug screens that have been positive for heroin in the past year!

* Results, line 7: "successful" is a tricky word here...seems like it depends on how success is defined. I'd consider removing or rewording.

**Response:** We classified this initiation as successful since the majority of women completed the induction with buprenorphine and continued treatment with buprenorphine despite also testing positive for other illicit substances (further discussed above). Prior attempts by the women were unsuccessful at initiating treatment with buprenorphine.

To clarify this point, we have changed the wording from “successful” to “completed induction onto maintenance sublingual buprenorphine doses confirmed by urine metabolites.” (75-77) in the results. We did not change the sentence in our discussion, “The majority of patients were successfully bridged onto sublingual buprenorphine therapy” (80-81) as we believe this sentence to accurately reflect our results.

* Discussion, line 4: I'm not sure how "unachievable" this would have been previously if women had continued using illicit opioids, which is the situation described for about half the study participants.

**Response:** Specifically, initiation of buprenorphine treatment was “unachievable” previously. The patients did not successfully initiate buprenorphine in their prior attempts and were not regularly taking buprenorphine for opioid blockade and replacement. However, after using the
patch, the majority of them returned at their follow-up visit using buprenorphine for opioid blockade on a daily schedule.

* Table comments:

- It would be useful to know how long women were admitted in the inpatient induction group.

**Response:** We have included this information into the “Reasons for Admissions” column of Table 2 in parentheses.

- There is no mention of the daily phone calls and how many resulted in successful contact. Was this tracked?

**Response:** The information was tracked and was not included in the table due to size considerations.

Daily attempts were made to contact patients leading up to their scheduled follow up appointment, which was scheduled within one week of initiation of induction. Thus, the attempts to contact patients varied depending on when their follow up appointment was scheduled. This data is shown in the table below.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of daily phone calls that resulted in successful contact leading up to scheduled follow up appointment (which was scheduled within 1 week of initiation of induction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N/A; bridged as inpatient</td>
</tr>
<tr>
<td>2</td>
<td>N/A; bridged as inpatient</td>
</tr>
<tr>
<td>3</td>
<td>N/A; bridged as inpatient</td>
</tr>
<tr>
<td>4</td>
<td>N/A; bridged as inpatient</td>
</tr>
<tr>
<td>5</td>
<td>2/2</td>
</tr>
<tr>
<td>6</td>
<td>3/6</td>
</tr>
<tr>
<td>7</td>
<td>3/3</td>
</tr>
<tr>
<td>8</td>
<td>2/4</td>
</tr>
</tbody>
</table>
Patient #2 should not have been included, correct? Since she had a COWs score >6?

**Response:** All women included in the study had COWS scores <6 prior to initiation. This column lists the maximum COWS score the patient experienced during the induction process onto buprenorphine after buprenorphine was initiated via the transdermal patch. Thus, patient #2 was still included.

Reviewer #3:

Comments to the author:

The authors present a timely research letter on the use of buprenorphine patch as a bridge to sublingual treatment for opioid use disorder in pregnancy. Although only a small case series, this letter addresses a serious issue with a less frequently discussed problem of induction. Any small improvement may pave the way for larger trials.

Introduction:

This is a good review of the challenges and pathophysiology of the induction process.

Line 53  In review of the citation Drug Alcohol Depend. 106 2018; 192:146-149. DOI: 10.1016/j.drugalcdep.2018.07.042 they list 64% adhere. I would recommend adding this type of quantitative background to put the challenge into context and contrast to your study.

**Response:** We thank you for this thoughtful comment – however, we are limited due to the word count constraints. With permission from the editors, we are happy to edit our discussion with a small inclusion:
Although illicit opioids were still concurrently used in half of patients at follow-up, the patch bridge allowed for the first step of sublingual buprenorphine initiation that was previously unachievable in a selective cohort of patients with more severe disease. *Ongoing opioid use concurrently with buprenorphine treatment is a frequent occurrence in patients with OUD that typically decreases over time as patients engage further in recovery services, with 64% adherence rates previously reported.* The results from this small series suggest that the patch may be a promising method of buprenorphine induction in pregnant patients with active OUD...

Methods:

Although retrospective this seems to be a descriptive case series. Were these patients previously failed induction on sublingual treatment? If not, a matched control group would be an interesting comparison, but the power may be too small for meaningful outcomes.

**Response:** The wording was corrected to case series. Yes, the patients had previously failed induction onto sublingual buprenorphine. We were unable to perform a meaningful matched cohort due to our small numbers of patched patients at this time.

Results:

Are there differences in success for treatment and induction with fentanyl vs other opioids like oxycodone or heroin? It looks like all included patients were fentanyl only. Was
there other confounder or challenges with polysubstance use as well?

**Response:** Fentanyl is 50 to 100 times more potent than morphine whereas heroin is only 10 times more potent than morphine. Given its potency, presumably it may be more difficult for individuals addicted to fentanyl than heroin to transition to medication assisted therapy. However, there are no studies that compare heroin versus fentanyl in this manner, and fentanyl makes up the vast majority of our current local illicit opioid supply. Polysubstance use was present in some of the patients included as well, but we choose not to address this in the case series due to our limited scope.

Table 1  I would recommend explaining the use of COWS scoring system and how it is used. It may not be familiar to all the readers.

**Response:** An explanation of COWS scoring system was included below the table 1 as a footnote.

Were there results for neonatal outcomes?

**Response:** We have neonatal outcomes tracked for 4/8 patients, as 1/8 delivered elsewhere and some patients are still pregnant. We did not include them in the manuscript as we wanted to focus specifically on the *maternal* outcome regarding buprenorphine induction, of which 3/8 occurred at the time of delivery and would not impact neonatal outcomes, in addition to the small number of available data points, and limited word count/tables for a research letter. However, if the editors feel that this information is helpful for the manuscript, we have included it here:
<table>
<thead>
<tr>
<th>Case</th>
<th>GA at delivery (weeks)</th>
<th>Weight (kg)</th>
<th>Intensive care unit admission</th>
<th>Neonatal abstinence syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32</td>
<td>1.5</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>3.4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>3.7</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>N/A, IUFD prior to admission</td>
<td>NA</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>3.1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>N/A, pregnancy ongoing</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>N/A, pregnancy ongoing</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>37, delivery occurred at outside hospital</td>
<td>2.3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

GA: gestational age; N/A: not applicable; IUFD: intrauterine fetal demise

Discussion:
Concise with clinical relevance.

STATISTICS EDITOR COMMENTS:

lines 24-25: A sample of n = 8 seems too few to generalize re: effectiveness of this method, especially since (lines 83-84) 1/2 of the patients in this series were still using illicit opioids, despite the patch, which may have contributed to the no or mild withdrawal symptoms (lines 75-76). In other words, need more measured, less conclusive statements re: effectiveness and amelioration of withdrawal symptoms based on this small sample.

Response: We have changed the wording: we have removed the word “effective” from the precis, and removed the word “successful” in our results to clarify that we specifically mean “completed induction onto maintenance sublingual buprenorphine doses.”
lines 72-73: With a sample size of only n = 8, estimation of SD is imprecise, Should simply state the mean or median with ranges for the maternal and gestational ages.

**Response:** This was corrected to show the median maternal and gestational age.

EDITOR COMMENT:

1. Thank you for submitting this work to Obstetrics and Gynecology. In your revision, it will be particularly important to address the comments from the statistical editor regarding toning down all statements related to demonstrating efficacy. As such, the Precis will need to be modified as well.

**Response:** We have removed “successful” in several place to tone down our statements and revised the precis to state:

“The buprenorphine transdermal patch can be used as a method of induction in pregnant patients with active opioid use disorder.”

2. Given that this is a case series of 8 patients, adding a control group would not allow for any definitive statements. Therefore, it is fine to just submit the revision as a case series (rather than adding a control group as requested by one of the reviewers).

**Response:** Thank you for this comment and we agree.