OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

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

Date: Oct 23, 2020
To: "F. Gary Cunningham" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-2650

RE: Manuscript Number ONG-20-2650

Acute Fatty Liver of Pregnancy

Dear Dr. Cunningham:

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 Nov 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a well written review of a rare, yet important, pregnancy related entity. The authors have done a great job of reviewing not only the history of this entity and its pathophysiology but the critical components of making the diagnosis. Tables 1, 2 and 3 as well as Figure 1 are most helpful for the clinician in determining management based on the correct diagnosis and Figures 4 and 5 are helpful in managing expectations of recovery in the patients postpartum.
This is a valuable summary for clinicians in helping them understand this entity and differentiate it from the more common conditions seen on the obstetrical suit. The tables and figures are useful tools.
The authors have done an excellent review that will be used frequently by clinicians caring for obstetrical patients.

Reviewer #2:

Nelson and colleagues submit a Clinical Expert Series article on acute fatty liver of pregnancy (AFLP). This Reviewer would request that the Authors address the following questions and comments:

Line 52. The word complications should be singular.

Line 67. This sentence tends to run on and could benefit from punctuation (e.g. comma, semicolon) or conversion to multiple sentences.

Line 94. Consider citing the years of Sibai's contemporaneous cases, for comparison.

Line 113. This sentence is unclear to this Reviewer; please further clarify.

Line 188. Consider describing the expected imaging findings, for each technique (i.e. US, CT, MRI).

Line 217. This should read "sequel" if singular and "sequelae" if pleural.

Line 233. The sentence should be further clarified.

Line 290. The term "neuroprophylaxis" may be confused with the neonatal indication; would "seizure prophylaxis" or "eclampsia prophylaxis" not be more appropriate?

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Line 324. An "analyte" generally refers to a chemical substance, rather than a cell (i.e. platelet).

Line 340. If magnesium sulfate is being administered, levels should be monitored.

Figure 1. It does not make sense (to this Reviewer) to start with a Basic Metabolic Panel (e.g. BUN, Cr, Na, K, CO2, Cl, glucose, Ca) plus LFTs plus LDH, then escalate lab evaluation if AFLP is suspected. Given the suspicion of AFLP on any given day is extremely rare, and given the stated importance of a prompt diagnosis, I would make the argument that ANY woman who presents with signs & symptoms potentially consistent with AFLP should receive ALL of the lab-work in the Figure, as soon as possible, in order to expedite diagnosis and treatment.

Figure 1. The Figure recommends testing for echinocytosis and nucleated RBCs. The former would be evident on peripheral smear, and the latter in an automated CBC, which should be explained in the text or the Figure.

Figure 4. To better appreciate the clinical ranges, consider a y-axis of 0-160 for cholesterol and 0-15 for bilirubin.

Figures 3, 4 & 5. Consider providing more information (i.e. reference, number of cases represented) in each of the figure legends.

Reviewer #3:

This paper by Nelson et al is a comprehensive review of acute fatty liver of pregnancy. The authors rightly concluded by stating that acute fatty liver of pregnancy is a condition commonly confused with pregnancy related hypertensive disorder, and requires prompt recognition, delivery planning, and management of associated multi-organ dysfunction. This paper was overall very well written. However, this paper has a number of issues that merit comments by the authors. These include:

General questions

1. Clinical implications - would the authors recommend universal screening for mothers with a prior history of AFLP?
2. It is important to stress that AFLP is a reversible form of hepatic failure that does not generally require liver transplantation, and with adequate support, these women regain full hepatic function.
3. Also important to discuss that early diagnosis, increased awareness and prompt supportive therapy with therapies like fluid support, antibiotics, 50% glucose, correction of coagulopathy, and renal support has dramatically improved the maternal survival from AFLP in the past few decades.
4. Again, important to stress that survivors of AFLP rarely have long-term sequelae.
5. A figure illustrating the feto-placental interphase, especially where the deficiencies are in AFLP with respect to LCHAD involvement in the beta oxidation of long-chain fatty acids, would be great.
6. Please discuss that LCHAD mutation is inherited in an autosomal recessive pattern, and discuss the role of prenatal genetic counseling in future pregnancies.

Abstract

Page 3; Lines 52-23: Although coagulation anomalies can be serious, it is important to understand that recovery of coagulation happens sooner than renal and hepatic function (as the kidney and liver are usually get the worst hit) - Usta IM, Barton JR, Amon EA et al. Acute fatty liver of pregnancy: an experience in the diagnosis and management of 14 cases. Am J Obstet Gynecol 1994; 171: 1342-7). The reviewer request that the authors correct this statement.

Introduction

Page 5, Line 94: The stated maternal mortality rate is quite conservative, and based on only one cited paper. The maternal mortality rate of AFLP in about 10-12.5% worldwide. Please review and revise.

Etiopathogenesis

Pages 5-6; Lines 97-122: This is a good summary of some of the molecular basis of AFLP. For more emphasis, the authors should give a detailed description of the molecular basis of AFLP, and the percentage that each mutation contributes to AFLP, as 1528 G>C (E474Q) mutation, though the commonest mutation in AFLP, contributes only about 19% of all cases of AFLP (Yang Z, Yamada J, Zhao Y. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. JAMA 2002; 288(17): 2163-2166).

Epidemiology and risk factors

Page 7, Line 141: Please the authors should state the commonest gestational ages in the 3rd trimester when acute fatty liver is most likely to occur.

Page 7, line 142: Please state the male:female ratio, as reported in prior studies (Fesenmeier MF, Coppage KH, Lambers DS et al. Acute fatty liver of pregnancy in 3 tertiary centers. Am J Obstet Gynecol 2005; 192: 1416-9).
Page 7, Lines 146-147: Please provide a reference for this statement
Page 7, lines 131-147: This is a good summary of the known epidemiology and risk factors for AFLP. Please add the following to this section:
"AFLP is commoner in primiparous women." Fesenmeier MF, Coppage KH, Lambers DS et al. Acute fatty liver of pregnancy in 3 tertiary centers. Am J Obstet Gynecol 2005; 192: 1416-9.
"While most cases occur in the 3rd trimester, some cases have been reported in the second trimester, with the earliest reported case of AFLP at 23 weeks of gestation. Very few cases of AFLP have been diagnosed in the postpartum period". (Suzuki S, Watanabe S, Araki T. Acute fatty liver of pregnancy at 23 weeks of gestation. BJOG 2001; 108: 223-4).

Clinical presentation and diagnosis:
Page 8, Line 153: It is not appropriate to state that the diagnosis of AFLP may be straightforward, as it is almost never straightforward, as most of the presenting symptoms of AFLP are non-specific, requiring a very high index of suspicion. Please re-structure this sentence.
Page 8, Lines 149-157: The authors should emphasize that the initial prodromal phase of AFLP's nonspecific symptoms can lasts upto 1-21 days, before clinical signs of jaundice and hepatorenal failure are detected.
Page 8, Lines 149-157: Also important to emphasize that pruritus (10% of cases), upper and lower gastrointestinal hemorrhage (upto 37% of cases) could be the associated symptoms.
Page 9, Line 172: Please complete this statement. Should read "three-fourths of the time", or "75% of cases had elevated ammonia levels".
Page 9, Line 184: What percentage of women require blood and blood products?
Page 9, Line 185-187: Please provide reference.
Page 10, Line 198-202: It is important to make the point that the histopathological diagnosis of AFLP is based on microvesicular fat in the cytoplasm of hepatocytes, but with no hepatic necrosis and periportal sparing. This distinguished AFLP from other fatty liver disorders, as well as other differential diagnoses of AFLP that are associated with necrosis of liver cells and periportal hepatic injury and necrosis (like pre-eclampsia and eclampsia).

Differential diagnoses:
Page 10, Line 213: Both HELLP syndrome and AFLP are very serious conditions and causes of maternal mortality. Please modify this statement.

Management:
Page 13, Lines 272-275: In addition to the principles of management mentioned, add 'Multidisciplinary approach for supportive care, usually with ICU involvement, and early liaison with gastroenterology, hematology, hepatology and transplant units, in case plasma exchange or consideration of liver transplant is required, like in cases where hepatic encephalopathy or fulminant hepatic failure develops".
Page 14, Lines 298-305: Agreed, the fetal condition is frequently non-reassuring, and there is the risk of coagulopathy with cesarean delivery. However, most cases of AFLP are diagnosed after delivery of the infant. Would you advocate for Obstetricians to watch a non-reassuring tracing that may never resolve even with fetal resuscitative measures? Please provide a balanced argument why vaginal delivery would be favored in this setting, taking the fetal heart rate tracing into consideration.
Page 15, Line 311: Provide a literature reference for the target fibrinogen range
Page 15, Lines 312-314: Provide a literature reference for choice of incisional types in AFLP.

Recurrence risk
Page 19, Lines 404-408: It is important to stress that the risk of recurrence of AFLP is dependent on the carrier status of the gene related to fatty acid oxidation. Recurrence risk is approximately 25%. Because 19% of AFLP is associated with mutation of the gene related to LCHAD - 1528 G>C (E474Q) mutation, a plausible recommendation would be that that offspring of mothers should be screened for this common mutation E474Q, in addition to any other associated mutations detected.

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

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

4. Tables, figures, and supplemental digital content should be original. The use of borrowed material (eg, lengthy direct quotations, tables, figures, or videos) is discouraged. If the material is essential, written permission of the copyright holder must be obtained.

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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. 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. 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. Please provide a word count.

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

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

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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%").

12. 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.

13. 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).

14. Please upload all figures as figure files on Editorial Manager.
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Figure 4: Okay.
Figure 5: Okay.

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file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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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 Nov 13, 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

_____

David Nelson, MD
Assistant Professor

Department of Obstetrics and Gynecology
Division of Maternal Fetal Medicine

November 2, 2020

Dwight Rouse, MD
Obstetrics & Gynecology

Re: Clinical Expert Series
Acute Fatty Liver of Pregnancy

To the Editors,

In response to your recommendations for revisions, we provide the following updated manuscript entitled “Acute Fatty Liver of Pregnancy” for consideration for publication in the Clinical Expert Series in *Obstetrics & Gynecology*. 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. This revised manuscript was developed in consultation with all co-authors, and it is being submitted with each author giving approval for the final form of the revision. Both a track change, and clean of the manuscript are included in this response. Please note that line references for revisions are included for the track change version of the manuscript.

Reviewer #1:

This is a well written review of a rare, yet important, pregnancy related entity. The authors have done a great job of reviewing not only the history of this entity and its pathophysiology but the critical components of making the diagnosis. Tables 1, 2 and 3 as well as Figure 1 are most helpful for the clinician in determining management based on the correct diagnosis and Figures 4 and 5 are helpful in managing expectations of recovery in the patients postpartum.
This is a valuable summary for clinicians in helping them understand this entity and differentiate it from the more common conditions seen on the obstetrical suit. The tables and figures are useful tools.
The authors have done an excellent review that will be used frequently by clinicians caring for obstetrical patients.

Thank you for the kind comments. No changes suggested.

Reviewer #2:

Nelson and colleagues submit a Clinical Expert Series article on acute fatty liver of pregnancy (AFLP). This Reviewer would request that the Authors address the following questions and comments:

Line 52. The word complications should be singular.

Ok. Line 52.

Line 67. This sentence tends to run on and could benefit from punctuation (e.g. comma, semicolon) or conversion to multiple sentences.

Ok-conversion to two sentences. Line 70.

Line 94. Consider citing the years of Sibai's contemporaneous cases, for comparison.

We have included statement citing data from 1994 to 2005. Line 97. Also, note Table 4.

Line 113. This sentence is unclear to this Reviewer; please further clarify.

Ok. We have revised. Line 117.

Line 188. Consider describing the expected imaging findings, for each technique (i.e. US, CT, MRI).

We have included previously reported criteria to diagnose fatty infiltration of the liver: (1) sonography: increased echogenicity; (2) CT scanning: subjectively decreased attenuation; and (3) MRI: increase signal in the T1-weighted image. Line 204.

Line 217. This should read "sequel" if singular and "sequelae" if pleural.

Sequelae now spelled correctly. Line 232.

Line 233. The sentence should be further clarified.

Symptomatology, such as fatigue, malaise, and pruritus, included for clarification. Line 248.

Line 290. The term "neuroprophylaxis" may be confused with the neonatal indication; would "seizure prophylaxis" or "eclampsia prophylaxis" not be more appropriate?

Magnesium sulfate infusion is begun for neuroprophylaxis eclampsia prophylaxis for those women who have evidence for preeclampsia which is seen in approximately 70% of patients. Line 307.

Line 296. The full intention of this sentence is somewhat unclear.

Sentence deleted. Line 311.

Line 324. An "analyte" generally refers to a chemical substance, rather than a cell (i.e. platelet).

We have clarified the sentence to state “platelet count.” Line 343.

Line 340. If magnesium sulfate is being administered, levels should be monitored.

We have included that serum magnesium levels are monitored. Line 355.

Figure 1. It does not make sense (to this Reviewer) to start with a Basic Metabolic Panel (e.g. BUN, Cr, Na, K, CO2, Cl, glucose, Ca) plus LFTs plus LDH, then escalate lab evaluation if AFLP is suspected. Given the suspicion of AFLP on any given day is extremely rare, and given the stated importance of a prompt diagnosis, I would make the argument that ANY woman who presents with signs & symptoms potentially consistent with AFLP should receive ALL of the lab-work in the Figure, as soon as possible, in order to expedite diagnosis and treatment.

We have included further clarification with the following, "If the initial clinical findings are suspicious for AFLP, then the whole battery of tests shown in Figure 1 are determined. In most cases, however, clinical findings and initial analyte determinations may be suggestive of AFLP at which time the targeted studies are performed." Line 167.

Figure 1. The Figure recommends testing for echinocytosis and nucleated RBCs. The former would be evident on peripheral smear, and the latter in an automated CBC, which should be explained in the text or the Figure.

We have included the statement in the Figure Legend, "Nucleated RBCs and echinocytes will be reported by CBC and peripheral smear." Line 567. Figure 1.

Figure 4. To better appreciate the clinical ranges, consider a y-axis of 0-160 for cholesterol and 0-15 for bilirubin.

We respectfully disagree and have chosen to leave the axis as is shown given the limited turnaround time of figure development, and this feature does not substantially change the plotted values.

Figures 3, 4 & 5. Consider providing more information (i.e. reference, number of cases represented) in each of the figure legends.

Figure 3 states N=67 women. Figures 4 and 5 vary with each time point. These were obtained from the 67 women in Figure 3.

Reviewer #3:

This paper by Nelson et al is a comprehensive review of acute fatty liver of pregnancy. The authors rightly concluded by stating that acute fatty liver of pregnancy is a condition commonly confused with pregnancy related hypertensive disorder, and requires prompt recognition, delivery planning, and management of associated multi-organ dysfunction. This paper was overall very well written. However, this paper has a number of issues that merit comments by the authors. These include:

General questions

1. Clinical implications - would the authors recommend universal screening for mothers with a prior history of AFLP?

Yes. Line 429.

2. It is important to stress that AFLP is a reversible form of hepatic failure that does not generally require liver transplantation, and with adequate support, these women regain full hepatic function.

We have added a statement for clarification. Line 419.

3. Also important to discuss that early diagnosis, increased awareness and prompt supportive therapy with therapies like fluid support, antibiotics, 50% glucose, correction of coagulopathy, and renal support has dramatically improved the maternal survival from AFLP in the past few decades.

We have emphasized that the composite maternal mortality is 13%, and the authors of cited publications stress that increased awareness and prompt supportive therapy are vital to maternal survival. They also stress that delivery is necessary to reverse ongoing organ dysfunction, but also recognize that cesarean delivery is more likely performed because of associated fetal compromise, and that operative delivery has more hemorrhagic complications. Line 413.

4. Again, important to stress that survivors of AFLP rarely have long-term sequelae.

See response to #2 and #3 above.

5. A figure illustrating the feto-placental interphase, especially where the deficiencies are in AFLP with respect to LCHAD involvement in the beta oxidation of long-chain fatty acids, would be great.

We considered including a figure, however, we were limited by space requirements.

6. Please discuss that LCHAD mutation is inherited in an autosomal recessive pattern, and discuss the role of prenatal genetic counseling in future pregnancies.

We have included a statement regarding “autosomal recessive” inheritance. Lines 104 and 427.

Abstract

Page 3; Lines 52-23: Although coagulation anomalies can be serious, it is important to understand that recovery of coagulation happens sooner than renal and hepatic function (as the kidney and liver are usually get the worst hit) - Usta IM, Barton JR, Amon EA et al. Acute fatty liver of pregnancy: an experience in the diagnosis and management of 14 cases. Am J Obstet Gynecol 1994; 171: 1342-7). The reviewer request that the authors correct this statement.

We have included a statement as suggested in the Abstract. Line 53.

Introduction

Page 5, Line 94: The stated maternal mortality rate is quite conservative, and based on only one cited paper. The maternal mortality rate of AFLP in about 10-12.5% worldwide. Please review and revise.

Sibai (2007) cited 7.5% in studies reported from 1994 to 2005, and we have modified the text to reflect this finding. Line 97. Table 4.

Etiopathogenesis

Pages 5-6; Lines 97-122: This is a good summary of some of the molecular basis of AFLP. For more emphasis, the authors should give a detailed description of the molecular basis of AFLP, and the percentage that each mutation contributes to AFLP, as 1528 G>C (E474Q) mutation, though the commonest mutation in AFLP, contributes only about 19% of all cases of AFLP (Yang Z, Yamada J, Zhao Y. Prospective screening for pediatric mitochondrial trifunctional protein defects in pregnancies complicated by liver disease. JAMA 2002; 288(17): 2163-2166).

We have modified the text to reflect this percentage. Line 125.

Epidemiology and risk factors

Page 7, Line 141: Please the authors should state the commonest gestational ages in the 3rd trimester when acute fatty liver is most likely to occur.

We have included gestational age as suggested. Line 146, cited references 18-20, 23.

Page 7, line 142: Please state the male:female ratio, as reported in prior studies (Fesenmeier MF, Coppage KH, Lambers DS et al. Acute fatty liver of pregnancy in 3 tertiary centers. Am J Obstet Gynecol 2005; 192: 1416-9).

Castro et al reference 19 cited 17/30 male fetus. Reference 19 included as citation for statement.

Page 7, Lines 146-147: Please provide a reference for this statement. Page 7, lines 131-147: This is a good summary of the known epidemiology and risk factors for AFLP. Please add the following to this section:
"AFLP is commoner in primiparous women." Fesenmeier MF, Coppage KH, Lambers DS et al. Acute fatty liver of pregnancy in 3 tertiary centers. Am J Obstet Gynecol 2005; 192: 1416-9.

Added “nulliparity” and have expanded the references as requested. Line 147.

"While most cases occur in the 3rd trimester, some cases have been reported in the second trimester, with the earliest reported case of AFLP at 23 weeks of gestation. Very few cases of AFLP have been diagnosed in the postpartum period". (Suzuki S, Watanabe S, Araki T. Acute fatty liver of pregnancy at 23 weeks of gestation. BJOG 2001; 108: 223-4).

Reference 20, Knight et al, noted 25% diagnosed postpartum.

Clinical presentation and diagnosis:

Page 8, Line 153: It is not appropriate to state that the diagnosis of AFLP may be straightforward, as it is almost never straightforward, as most of the presenting symptoms of AFLP are non-specific, requiring a very high index of suspicion. Please re-structure this sentence.

Done. Line 156.

Page 8, Lines 149-157: The authors should emphasize that the initial prodromal phase of AFLP's nonspecific symptoms can lasts upto 1-21 days, before clinical signs of jaundice and hepatorenal failure are detected.

Done. Line 160.

Page 8, Lines 149-157: Also important to emphasize that pruritus (10% of cases), upper and lower gastrointestinal hemorrhage (upto 37% of cases) could be the associated symptoms.

Done. Line 163..

Page 9, Line 172: Please complete this statement. Should read "three-fourths of the time", or "75% of cases had elevated ammonia levels".

Done. Line 182.

Page 9, Line 184: What percentage of women require blood and blood products?

The number is not known, or specifically reported.

Page 9, Line 185-187: Please provide reference.

Reference 32 added to the text. Line 197.

Page 10, Line 198-202: It is important to make the point that the histopathological diagnosis of AFLP is based on microvesicular fat in the cytoplasm of hepatocytes, but with no hepatic necrosis and periportal sparing. This distinguished AFLP from other fatty liver disorders, as well as other differential diagnoses of AFLP that are associated with necrosis of liver cells and periportal hepatic injury and necrosis (like pre-eclampsia and eclampsia).

Done. Line 213. Also, please refer to Line 86 where this is also further discussed.

Differential diagnoses:

Page 10, Line 213: Both HELLP syndrome and AFLP are very serious conditions and causes of maternal mortality. Please modify this statement.

Done. Line 227.

Management:

Page 13, Lines 272-275: In addition to the principles of management mentioned, add 'Multidisciplinary approach for supportive care, usually with ICU involvement, and early liaison with gastroenterology, hematology, hepatology and transplant units, in case plasma exchange or consideration of liver transplant is required, like in cases where hepatic encephalopathy or fulminant hepatic failure develops".

Done. Line 291.

Page 14, Lines 298-305: Agreed, the fetal condition is frequently non-reassuring, and there is the risk of coagulopathy with cesarean delivery. However, most cases of AFLP are diagnosed after delivery of the infant. Would you advocate for Obstetricians to watch a non-reassuring tracing that may never resolve even with fetal resuscitative measures? Please provide a balanced argument why vaginal delivery would be favored in this setting, taking the fetal heart rate tracing into consideration.

We have added that vaginal delivery is preferred with a reassuring fetal status. Line 321.

Page 15, Line 311: Provide a literature reference for the target fibrinogen range

There is not a reference for this recommendation, and we made it clear that this is our recommendation from our experiences. Line 330.

Page 15, Lines 312-314: Provide a literature reference for choice of incisional types in AFLP.

See comment above to Page 15, Line 311 comment.

Recurrence risk

Page 19, Lines 404-408: It is important to stress that the risk of recurrence of AFLP is dependent on the carrier status of the gene related to fatty acid oxidation. Recurrence risk is approximately 25%. Because 19% of AFLP is associated with mutation of the gene related to LCHAD - 1528 G>C (E474Q) mutation, a plausible recommendation would be that that offspring of mothers should be screened for this common mutation E474Q, in addition to any other associated mutations detected.

We cannot find a reference for a 25% recurrence risk. Intuitively, autosomal recessive inheritance risk is 25%, however, this has not been reported in the literature. We do recommend that screening for fatty oxidation disorders be considered. Line 427.

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We do not have any financial conflicts to report in the development of this manuscript.

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Figure 3 is cited from references 29 and 30.

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.

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We respectfully request the Editors' allow inclusion of the Tables and Figures for completeness of this report.

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References reconciled. Reference 34, the American College of Obstetricians and Gynecologists: Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122:1122-31, was cited for hepatic hematoma management, and is still a citation relevant for this finding as "hepatic hematoma," is not discussed in the current ACOG practice bulletin, No. 222, Gestational Hypertension and Preeclampsia. The current reference can be found within PubMed, PMID: 24150027. If the Editors request further reconciliation, we would be glad to do so.

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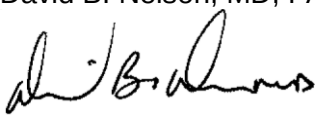
Thank you again for the opportunity to revise our manuscript and incorporate the feedback from the Reviewers. The inclusion of their suggested comments has strengthened our report, and we hope will provide meaningful information to the readership in the management of this rare, but significant, medical complication.

David B. Nelson, MD, FACOG



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