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

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

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

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

Date: Aug 26, 2022
To: "Luis D. Pacheco" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1339

RE: Manuscript Number ONG-22-1339

Inherited bleeding disorders in pregnancy

Dear Dr. Pacheco:

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

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

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

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

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 16, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present an expert review on bleeding disorders in pregnancy with specific focus on von Willebrand Disease (vWD) and hemophilia. The authors discuss available evidence and provide management recommendations for optimization of maternal and fetal-neonatal outcomes.

I have the following specific questions/comments:

1. Intro: Recommend the addition of an introduction paragraph with a brief overview of the information to be discussed in this review and a stated objective for the review.

2. Lines 52-55: These epidemiology statistics would be amenable to presentation in a table. Alternatively, consider moving the prevalence statistics for vWD to later discussion of vWD (starting lines 144) and focus on an introductory paragraph (as recommended above).

3. Lines 159-166: As the authors discuss changes in platelet levels in pregnancy (lines 138-141), it would be worthwhile to comment on differences in thresholds for diagnosis in pregnancy versus outside of pregnancy.

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5. Lines 210-212: There is known controversy over route of delivery for a pregnancy with a hemophilia affected fetus. The stated recommendation for cesarean delivery reflects a single guideline and is absent the nuance of available data. This statement should be amended. Recommend inclusion of absolute numbers for intracranial hemorrhage (reported 2-4%), presentation of studies/data on mode of delivery and ICH, and discussion of shared decision making.

6. Lines 292-293: Consider summarizing the available products on the market, or place the product discussion into a table.

7. Lines 295-298: This may be specific to the institutions where I practice, but often real time results for activity levels are not available (24-48h result delay); can the authors comment on best practices for scenarios with unknown levels at term (e.g., patient comes in laboring without values or lab delay in results) or in the postpartum period?

8. Lines 302-304: Can the authors provide data on absolute rates of neonatal bleeding complications for neonates with vWD? This would better provide an understanding to clinicians about the absolute risks for patient counseling.

9. Line 306/Figure 2: Nice summary figure outlining vWD management. Consider adding a sentence about potential utility (or lack thereof) of vWF activity levels obtained prior to the third trimester and if bleeding complications arise during pregnancy.

10. Lines 324-330: Recommend revision of this section. While a cesarean delivery is a reasonable option in appropriately counseled patients, the authors do not present adequate data to support their conclusion of recommending planned cesarean in all patients. Stating an 8-fold increased risk (line 326) in isolation without absolute rates or discussion of the nuance of studies (e.g., inclusion of operative delivery) is misleading. Recommend presentation of additional data on ICH by mode of delivery and inclusion of absolute rates of ICH (from Kulkarni et al; consider additional studies: Andersson NG et al).

11. Lines 330-340: Recommend removal of this section. The references (line 335, reference 43 and 44) are not appropriate for the outlined discussion; these address mode of delivery for term, breech singletons and twin deliveries, respectively.

12. Lines 345-349: Recommend discussion of data or citation to support stated recommendations.

Overall, this manuscript provides an informative review of diagnosis and management of vWD, hemophilia, and other bleeding disorders in pregnancy. Generally, the review would be strengthened by further presentation of specific studies informing the recommendations. This is particularly necessary in light of the authors strong recommendation for cesarean delivery in all pregnancies with a male affected fetus with hemophilia.

Reviewer #2: "Inherited bleeding disorders in pregnancy", submitted for publication in the "Clinical Expert Series", is a review of the most common types of bleeding disorders affecting pregnant people. The review of each disorder- including pathophysiology, inheritance, treatment- is clear and well-written. The level of detail, the quality of the disease review, and the order in which the disorders are reviewed are outstanding. However, the review of obstetric management that ensues needs attention. This part of the review reads a bit like a chapter review of a seemingly straightforward topic, when in fact there are layers of controversy, of different management strategies, and of need for further research. "Current guidelines" is a frequently used phrase, but in fact, there are many different guidelines from different sources on many of these matters, including guidelines from obstetric organizations, such as RCOG, ACOG, SMFM, and SOAP (Soc for OB Anesth), which do not always agree. A much more thorough and detailed discussion of acute obstetric care issues- from timing and mode of delivery, to neuraxial anesthesia access should occur here, as it is often not straightforward to make care plans for these patients.

See the specific comments below. Additionally, as a minor comment- throughout the review the words "her" and "woman" should be made to be more inclusive as often possible ("person, patient, etc.).

Abstract:
Line 40 misspelling of "anticipated"

Page 3, Line 58 change "has" to "have"

Page 4, line 70: clarify that G1b-Ix-V is a glycoprotein complex made of 3 subunits, and is the most abundant platelet adhesion receptor

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the context of an affected male fetus. While this is the recommendation of the National Hemophilia Foundation, recommendations from other groups and experts vary, and this continues to be an area of controversy. Consideration of a woman's a-priori obstetrical risks are paramount to proper counseling on mode of delivery. As this is meant to be a review of bleeding disorders generally, I think a much more nuanced approach to the mode of delivery discussion in the context of an affected male infant is warranted. It is clear that obstructed labor, use of vacuum and use of forceps increase the risk of ICH, however, it is unclear currently what the level of risk is in the context of a normal, unassisted labor course. For example, I woman with 2 prior recent uncomplicated vaginal deliveries of female infants may not be better served by a cesarean for a 3rd baby, even if a known male hemophiliac. These conversations are complex, and whether to perform a major abdominal surgery on a woman in this context must take into account details her history, as well as her preferences.

Page 11, line 222: important to state that pregnancy is a hypercoaguable state, and that use of rFVIIa should be carefully weighed against increased risk of thrombosis, and used only under the supervision of Hematologists and/or MFM providers with expertise in this area. Care should be made to ensure that the standard uterotonics and PPH protocols are used first, with consideration of use of FFP as well. rFVIIa should really only be considered in the event of life-threatening hemorrhage.

Pages 12-16:
- Discussion on management of labor and delivery should be more specific, and more complete. Controversies about re: the safety of neuraxial anesthesia for people with VWD, and it is well-known that neuraxial anesth is not offered to many people with VWD even with VWF >50%. A more substantial discussion is warranted.
--The use of prolonged TXA treatment in the first several days postpartum for people with VWD has not been shown to be safe from a thrombotic perspective as of yet in any large trials. Any use of TXA in pregnancy or the immediate postpartum period outside of the dosing using in the WOMAN Trial should be discussed as expert opinion based on low-certainty evidence.
- As for the discussion re: mode of delivery in the context of hemophilia, as I stated earlier, this should be a much deeper dive into the literature re: recommendations for and against a planned, unlabored cesarean with a male fetus at risk for ICH.

Page 17, Conclusions:
There is much research to be done to better understand how to best care for pregnant people with bleeding disorders, and the Conclusions should better reflect some of the research and knowledge gaps that currently exist. The issue of what the "right" factor level is for procedures and neuraxial anesth in particular is an area that deserves more discussion. Additionally, the importance of a multidisciplinary team should not first appear in the conclusions. Caring for these patients can be complex, and the importance of ongoing multidisciplinary care and communication between providers cannot be understated, and deserves earlier discussion (in the introduction and throughout the review).

Reviewer #3: The authors provide a comprehensive review of characterization and management of inherited disorders in pregnancy in this manuscript.

Precis: appropriate

Abstract: Consider removing some of the additional detail in lines 34-36 "if there has been a DDAVP challenge..". It makes the sentence difficult to follow. This level of specificity can remain in the body of the main text.

Main Text: Overall this review is comprehensive, but could benefit form adding subheadings and removing repetitive text.
1. In lines 55-58 the authors offer two interpretations of prevalence. For the readers sake please consider choosing the best estimate recognizing there will always be limitations to this data. The current way this information is presented is a little confusing.

2. Consider introducing the stages of clot formation before introducing them in parentheses after sentences (section "normal hemostasis").

3. Authors can simply put "Figure 1" in parentheses in Line 89.

4. Protein S is introduced for the first time in line 94 with no prior or further mention. Either provide context of where this fits into the larger picture of coagulation or remove.

5. The bulleted items in lines 104-115 take up a lot of space and could be better suited for a table.

6. Please consistently underline and emphasize text throughout. For example, underline "Type 3 VWD" in line 171. Also highlight the "qualitative dysfunction" in line 170.

7. Overall VWD paragraph is very long (2 pages) and could be shortened or broken up. (starts at line 145)

8. Subtitles would be particularly helpful under the "other inherited clotting factors" section.

9. Management strategies are introduced in lines 242-244 and again in lines 252-255 before the official management section of the manuscript. If you want to maintain this information in its current location consider changing the title of this section or move to the management portion of the text.

10. Recommendations in lines 265-269 appear to be at best expert opinion. Are there any other citations aside from #27 that support this practice?

11. Lines 270-272 represent a one sentence paragraph. Please try to incorporate with the text above for formatting.

12. In lines 285-286 is there a goal sodium or a threshold of hyponatremia/hypernatremia they should look out for?

13. Its unclear where the recommendation regarding TXA comes from in lines 299-301. The reference does not seem to correspond to this recommendation. Please provide a clear citation for this recommendation.

14. The portion of the manuscript regarding delivery mode is long and reads as expert opinion. I think this could be shortened considerably and made more to the point by removing speculative writing.

15. A reference is needed in line 322.

16. Some blood products may be difficult to come by. Early and clear communication with blood bank should be emphasized to ensure availability of required products.

17. In line 353 what is "similar to VWD?" Which disorder are the authors referring to.

Figures and Tables
1. Table 1 is too wordy. Please reduce text to minimum required. Other import notes can be added to the main text or as a footnote.

2. Please ensure management regarding TXA in Figure 2 and length of time to monitor levels in Figure 3 are based on data and if expert opinion please make that clear.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

5. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

6. Permissions: Thank you for uploading permission for Figure 1!

Are Figures 2 and 3 original to the manuscript? If yes, both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers have online systems for submitting permissions requests; please consult the publisher directly for more information.

7. 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.

8. Length: Clinical Expert Series articles should be no longer than 25 double-spaced pages (approximately 6,250 words). Figures are not considered in the final page count.

9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

10. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Clinical Expert Series: 300 words

11. 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.

12. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

13. Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. 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 formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

16. Figure 1-3: Please upload as figure files on Editorial Manager.

17. 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.

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 as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision.

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 16, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD, MD
Associate Editor, OB

_____

utmb Health

SCHOOL OF MEDICINE
DEPARTMENT OF OBSTETRICS & GYNECOLOGY

Luis D. Pacheco, MD
Professor

[redacted]

September 13, 2022

Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024-2188

Dear Editors:

Thank you for your review of our manuscript titled "Inherited bleeding disorders in pregnancy" for publication in your journal. Our point-by-point response to each of the received comments is attached at the end of this letter.

Please find the revised version of the manuscript attached.

This article has not been previously published and is not currently under consideration for publication by any other journal. Each of the authors made substantial contributions to the drafting of the manuscript, and each has confirmed they have no conflicts of interest.

For questions concerning this manuscript, please feel free to contact me.

Sincerely,

Luis D. Pacheco, MD
Departments of Obstetrics & Gynecology and Anesthesiology
The University of Texas Medical Branch at Galveston

REVIEWER COMMENTS:

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I have the following specific questions/comments:

1. Intro: Recommend the addition of an introduction paragraph with a brief overview of the information to be discussed in this review and a stated objective for the review.

R/ Agree with comment, we have added an introduction addressing the recommendations of the reviewer.

2. Lines 52-55: These epidemiology statistics would be amenable to presentation in a table. Alternatively, consider moving the prevalence statistics for vWD to later discussion of vWD (starting lines 144) and focus on an introductory paragraph (as recommended above).

R/ Agree with comment. We have shortened these initial prevalence values and provided just a quick summary of them as part of the introduction.

3. Lines 159-166: As the authors discuss changes in platelet levels in pregnancy (lines 138-141), it would be worthwhile to comment on differences in thresholds for diagnosis in pregnancy versus outside of pregnancy.

R/ Agree with comment, however, we are not addressing platelet disorders in this manuscript. We would limit the discussion as it is the text to comply with the journal's word limit requirements.

4. Lines 159-173: This section on vWD types could be condensed, particularly as the same information is also presented in Table 1.

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R/ The section regarding route of delivery for a pregnancy with a male fetus affected with hemophilia has been extensively revised and addresses the reviewers' concerns regarding

nuance, inclusion of absolute numbers ICH, and discussion of shared decision making. The absolute rates of ICH by mode of delivery from Kulkarni et al have been included. Andersson et al has been cited.

6. Lines 292-293: Consider summarizing the available products on the market, or place the product discussion into a table.
R/ We have added the commercial names of the products. Since they are all similar, we do not believe a table or further discussion is warranted as it will be out of the scope of the present paper.

7. Lines 295-298: This may be specific to the institutions where I practice, but often real time results for activity levels are not available (24-48h result delay); can the authors comment on best practices for scenarios with unknown levels at term (e.g., patient comes in laboring without values or lab delay in results) or in the postpartum period?

R/ We agree with the comment, unfortunately availability of test results certainly vary by center. We recommend the use of the most widely available tests in our algorithms. We cannot offer management recommendations in the absence of laboratory results. This is why we strongly recommend in the manuscript obtaining a baseline profile in the third trimester to use as a surrogate at the time of delivery if turnaround of test results is anticipated to be prolonged.

8. Lines 302-304: Can the authors provide data on absolute rates of neonatal bleeding complications for neonates with vWD? This would better provide an understanding to clinicians about the absolute risks for patient counseling.

R/ We have added a reference of a case series involving VWD and ICH in neonates.

9. Line 306/Figure 2: Nice summary figure outlining vWD management. Consider adding a sentence about potential utility (or lack thereof) of vWF activity levels obtained prior to the third trimester and if bleeding complications arise during pregnancy.

R/ Agree with comment. We added a comment in the text addressing the utility of levels prior to the third trimester in patients with active bleeding or undergoing invasive procedures before delivery.

10. Lines 324-330: Recommend revision of this section. While a cesarean delivery is a reasonable option in appropriately counseled patients, the authors do not present adequate data to support their conclusion of recommending planned cesarean in all patients. Stating an 8-fold increased risk (line 326) in isolation without absolute rates or discussion of the nuance of studies (e.g., inclusion of operative delivery) is misleading. Recommend presentation of additional data on ICH by mode of delivery and inclusion of absolute rates of ICH (from Kulkarni et al; consider additional studies: Andersson NG et al).

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R/We have retained this section in this version of the manuscript as the studies cited do address maternal risks by mode of delivery, but we have clarified that the studies were not performed in hemophilia carriers.

12. Lines 345-349: Recommend discussion of data or citation to support stated recommendations.

R/ This section has been revised. Additional data and citations have been added.

Overall, this manuscript provides an informative review of diagnosis and management of vWD, hemophilia, and other bleeding disorders in pregnancy. Generally, the review would be strengthened by further presentation of specific studies informing the recommendations. This is particularly necessary in light of the authors strong recommendation for cesarean delivery in all pregnancies with a male affected fetus with hemophilia.

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See the specific comments below. Additionally, as a minor comment- throughout the review the

words "her" and "woman" should be made to be more inclusive as often possible ("person, patient, etc.).

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R/ Agree, corrected in text.

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R/ We have changed this section and added an introduction as requested by reviewer #1. This wording is not present anymore in the updated version.

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R/ Added comment.

Page 5, lines 91-96: Need to split out pregnancy from the postpartum period. While the statements made here are correct as they relate to pregnancy, they are incorrect as they relate to the postpartum period. There is a rapid return towards the non-pregnant state, with VWF decreasing, and similarly for FVIII and fibrinogen. Further, fibrinolytic activity is increased nearly immediately.

R/ Agree with comment, we have removed "postpartum" from the statement.

Page 9, line 188: as this is a review of bleeding d/o in women, important to point out that the frequency of hemophilia carrier status is unknown, and estimates range from 1.5-5 carriers for every male hemophiliac

R/ Agree with comment, this is consistent with the statement in the manuscript "for every 100 males with hemophilia, there were 156 female carriers.

Page 10, line 208: There have been cases of severely affected female hemophiliacs at birth, with a bleeding phenotype due to reasons listed earlier (lionization, etc.), and some experts recommend caution at delivery in the context of an obligate carrier- i.e. avoiding traumatic delivery, avoiding instrumented delivery (ref: d'Oiron et al.; Haemophilia, 2021; 27)

R/ We agree. The following has been added, " the same precautions should be observed as with any fetus with a possible mild or moderate bleeding disorder (avoidance of invasive procedures such as use of fetal scalp clips, and if possible, operative vaginal deliveries)."

Page 10, line 211: The authors should use caution in stating that "current guidelines recommend a cesarean delivery" in the context of an affected male fetus. While this is the recommendation

of the National Hemophilia Foundation, recommendations from other groups and experts vary, and this continues to be an area of controversy.

R/ We now clearly state instead of "current guidelines," that the recommendation for cesarean delivery comes from the Medical and Scientific Advisory Committee of the National Hemophilia Foundation. Furthermore, we acknowledge that there has been controversy regarding the mode of delivery and clearly state that we recommend cesarean delivery as opposed to stating, "guidelines recommend."

R/ Consideration of a woman's a-priori obstetrical risks are paramount to proper counseling on mode of delivery. As this is meant to be a review of bleeding disorders generally, I think a much more nuanced approach to the mode of delivery discussion in the context of an affected male infant is warranted. It is clear that obstructed labor, use of vacuum and use of forceps increase the risk of ICH, however, it is unclear currently what the level of risk is in the context of a normal, unassisted labor course. For example, I woman with 2 prior recent uncomplicated vaginal deliveries of female infants may not be better served by a cesarean for a 3rd baby, even if a known male hemophiliac. These conversations are complex, and whether to perform a major abdominal surgery on a woman in this context must take into account details her history, as well as her preferences.

R/ We agree and we have added the following to the manuscript, "We do recognize that consideration of a woman's a-priori obstetrical risks are paramount to proper counseling regarding mode of delivery and that after appropriate counseling, in the context of shared decision making, some women may elect to proceed with planned vaginal delivery, especially a parous women who have had at least one or more successful spontaneous vaginal deliveries…"

Page 11, line 222: important to state that pregnancy is a hypercoaguable state, and that use of rFVIIa should be carefully weighed against increased risk of thrombosis, and used only under the supervision of Hematologists and/or MFM providers with expertise in this area. Care should be made to ensure that the standard uterotonics and PPH protocols are used first, with consideration of use of FFP as well. rFVIIa should really only be considered in the event of life-threatening hemorrhage.

R/ The use of low dose activated Factor VII is standard for patients with factor VII deficiency and bleeding. This is in contrast with the use of this agent in patients with no congenital bleeding disorder suffering from post-partum hemorrhage. We are not referring to the use of recombinant activated factor VII in patients not suffering from congenital deficiency of factor VII.

Pages 12-16:
- Discussion on management of labor and delivery should be more specific, and more complete. Controversies about re: the safety of neuraxial anesthesia for people with VWD, and it is well-known that neuraxial anesth is not offered to many people with VWD even with VWF >50%. A more substantial discussion is warranted.
--The use of prolonged TXA treatment in the first several days postpartum for people with VWD

has not been shown to be safe from a thrombotic perspective as of yet in any large trials. Any use of TXA in pregnancy or the immediate postpartum period outside of the dosing using in the WOMAN Trial should be discussed as expert opinion based on low-certainty evidence.
- As for the discussion re: mode of delivery in the context of hemophilia, as I stated earlier, this should be a much deeper dive into the literature re: recommendations for and against a planned, unlabored cesarean with a male fetus at risk for ICH.

R/ We believe the most thorough section of the article is the intra partum management. The use of neuraxial anesthesia with factor VIII and VWF activity above 0.5 IU/mL is recommended by multiple groups including ASH, ISTH, NHF, WFH, and the RCOG. We have added a paragraph highlighting the importance of multidisciplinary counseling at the time of analgesia discussion for delivery. Similarly, all the previously cited organizations recommend the use of oral TXA during the postpartum period. We do not agree with the reviewer in extrapolating TXA dosages used during the WOMAN trial to a population of women with congenital bleeding disorders. The WOMAN trial included women with active bleeding, received intravenous TXA, and had no congenital bleeding disorders. The available literature does not suggest a risk of clotting with the use of postpartum oral TXA in women with congenital bleeding disorders.

Page 17, Conclusions:
There is much research to be done to better understand how to best care for pregnant people with bleeding disorders, and the Conclusions should better reflect some of the research and knowledge gaps that currently exist. The issue of what the "right" factor level is for procedures and neuraxial anesth in particular is an area that deserves more discussion. Additionally, the importance of a multidisciplinary team should not first appear in the conclusions. Caring for these patients can be complex, and the importance of ongoing multidisciplinary care and communication between providers cannot be understated, and deserves earlier discussion (in the introduction and throughout the review).

R/ Agree with comment. The comment included in our conclusion regarding the optimal factor level threshold at the time of invasive procedures obviously includes neuraxial anesthesia. We have added a comment in the introduction about the importance of assembling a multidisciplinary team when caring for these patients.

Reviewer #3: The authors provide a comprehensive review of characterization and management of inherited disorders in pregnancy in this manuscript.

Precis: appropriate

Abstract: Consider removing some of the additional detail in lines 34-36 "if there has been a

DDAVP challenge..". It makes the sentence difficult to follow. This level of specificity can remain in the body of the main text.

R/ Agree with comment, we have removed the sentence form the abstract.

Main Text: Overall this review is comprehensive, but could benefit form adding subheadings and removing repetitive text.

1. In lines 55-58 the authors offer two interpretations of prevalence. For the readers sake please consider choosing the best estimate recognizing there will always be limitations to this data. The current way this information is presented is a little confusing.

R/ Agree with comment, this paragraph has been removed an introduction has been included in the text.

2. Consider introducing the stages of clot formation before introducing them in parentheses after sentences (section "normal hemostasis").

R/ We opted not to discuss in depth the different stages of clotting due to manuscript length requirements. These parentheses are only the basic steps of platelet activity. We believe it is clear and concise the way it is in the original manuscript.

3. Authors can simply put "Figure 1" in parentheses in Line 89.

R/ Agree, change has been made in text.

4. Protein S is introduced for the first time in line 94 with no prior or further mention. Either provide context of where this fits into the larger picture of coagulation or remove.

R/ We do not agree with the comment, this statement is in the text just to add to the fact that pregnancy is a hypercoagulable state. We believe it is justified to leave in the text as originally written.

5. The bulleted items in lines 104-115 take up a lot of space and could be better suited for a table.

R/ Agree with comment, we have removed the bullets and kept the information as part of the text.

6. Please consistently underline and emphasize text throughout. For example, underline "Type 3 VWD" in line 171. Also highlight the "qualitative dysfunction" in line 170.

R/ Agree, changes have been added to the text.

7. Overall VWD paragraph is very long (2 pages) and could be shortened or broken up. (starts at line 145)

R/ We have shortened the section as some information is on Table 1.

8. Subtitles would be particularly helpful under the "other inherited clotting factors" section.

R/ The discussion of other inherited bleeding disorders is very short, we don't believe enough contents is presented on each topic to warrant a dedicated section for them. This is not the goal of the article as stated in the text.

9. Management strategies are introduced in lines 242-244 and again in lines 252-255 before the official management section of the manuscript. If you want to maintain this information in its current location consider changing the title of this section or move to the management portion of the text.

R/ These management strategies are cited in this section as they relate to these specific diseases ("other inherited clotting factor deficiencies" and "Inherited platelet disorders"). The following section (Maternal management at the time of delivery) focuses only on VWD and hemophilia, as stated in the text.

10. Recommendations in lines 265-269 appear to be at best expert opinion. Are there any other citations aside from #27 that support this practice?

R/ We clearly state on lines 262-265 of the original manuscript that any recommendation regarding management is based on observational studies and expert opinion. We have added a second reference to the statement.

11. Lines 270-272 represent a one sentence paragraph. Please try to incorporate with the text above for formatting.

R/ Agree with comment, changed has been made in the text.

12. In lines 285-286 is there a goal sodium or a threshold of hyponatremia/hypernatremia they should look out for?
R/ The most important thing is just to avoid hyponatremia, no specific targets are needed. A sentence has been added to the manuscript recommending keeping levels within the normal range.

13. Its unclear where the recommendation regarding TXA comes from in lines 299-301. The reference does not seem to correspond to this recommendation. Please provide a clear citation for this recommendation.

R/ The reference is in the following sentence, when the recommended dosage for TXA is specified (Reference 37, 2021 guidelines from the ASH, ISTH, NHF, and WFH.

14. The portion of the manuscript regarding delivery mode is long and reads as expert opinion. I think this could be shortened considerably and made more to the point by removing speculative writing.

R/ We disagree with this statement. This is the most important portion of the article, we strived to provide step by step recommendations to include most of the potential situations that could arise during labor and delivery. We believe clinicians appreciate articles that are practical and applicable to their practice.

15. A reference is needed in line 322.

R/ Agree, references added.

16. Some blood products may be difficult to come by. Early and clear communication with blood bank should be emphasized to ensure availability of required products.

R/ Agree with comment. We recommend in our manuscript involvement of the blood bank as part of the multidisciplinary team caring for these patients.

17. In line 353 what is "similar to VWD?" Which disorder are the authors referring to.

R/ We mean that just like in VWD, in hemophilia the use of post-partum TCXA is also recommended.

Figures and Tables

1. Table 1 is too wordy. Please reduce text to minimum required. Other import notes can be added to the main text or as a footnote.

R/ In addressing another reviewer, it was suggested that we shorten the text as most of the information was on the table. We did shorten the text. The table is detailed and provides all information needed in a simple and friendly way to readers.

2. Please ensure management regarding TXA in Figure 2 and length of time to monitor levels in Figure 3 are based on data and if expert opinion please make that clear.

R/ We clearly state on lines 262-265 of the original manuscript that any recommendation regarding management is based on observational studies and expert opinion. We have added a second reference confirming recommended length of levels above 0.5 IU/mL following vaginal or cesarean delivery.