

# 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.*

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:  
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**Date:** 01/20/2023  
**To:** "Ruican Dan" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-22-2175

RE: Manuscript Number ONG-22-2175

Confirmation of Fetal Heart Malformations in the First Trimester Fetuses using Three-Dimensional Histological Autopsy

Dear Dr. Dan:

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

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

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

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

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by 02/10/2023, we will assume you wish to withdraw the manuscript from further consideration.

#### EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics & Gynecology. If you elect to submit a revision for consideration, please format as a Procedures and Instruments article, and follow the author instructions for that type of submission, which will result in a reduction in word count.

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

\*\*\*Figures: Note that these figures will not fit within a printed manuscript. Please move several to supplemental digital content.

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\* Figure 7: Is this figure original to the manuscript? Permission may be required. Please remove A-C labels, these will be added back per journal style. Please upload as a figure file on Editorial Manager.

\* Figure 8: Please remove A-D labels, these will be added back per journal style. Note that we cannot break A-D into A1, A2, etc. Please upload as a figure file on Editorial Manager.

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\* Figure 11: Please remove A-C labels, these will be added back per journal style. Note that we cannot break A-D into A1, A2, etc. Please upload as a figure file on Editorial Manager.

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#### REVIEWER COMMENTS:

##### Reviewer #1:

Thank you for a well written narrative about the meticulous reconstruction of abnormal embryonic human structures to confirm early imaging findings of cardiac anomalies. The precision of your methods and the resulting images and interpretation are nothing short of amazing. Please consider the following comments and questions.

What is the incidence of serious congenital heart defects among live births and under what circumstances might discovery of such abnormalities intrapartum lead to a decision to terminate the pregnancy? What options are available?

From a practical point of view how desirable would it be to have the ability to conduct your diagnostic confirmatory methodology available widely (regionally or globally)? Would the cost of such testing be a financial burden to the individuals involved?

What are the clinical and public health implications of such confirmatory testing for the general public especially in countries with laws that limit or ban first trimester pregnancy termination except in certain circumstances?

Do you think because of the basic science importance of your efforts you would be best served by submitting your work to a specialty journal dealing more with clinical pathology, clinical imaging, cardiology, or human embryology?

##### Reviewer #2:

In the manuscript under review, we evaluate the results of a case series evaluating the use of three-dimensional reconstruction of histology slides following first-trimester termination for suspected congenital heart defects. The authors had 6 cases in which this novel technique allowed them to detect minor anomalies not previously seen.

A few comments on the manuscript are as follows:

#### ABSTRACT

1. No major issues were noted

#### INTRODUCTION

2. No clear hypothesis is stated by the authors

#### METHODS

3. Line 66-71 - at what gestational age were these ultrasound examinations done?

## RESULTS

4. Line 143 - why was an isolated VSD during the first trimester considered an anomaly? Most of these close on their own

## DISCUSSION

5. As an overall comment, do the authors have any data on this technique in cases of first-trimester autopsy not related to cardiac anomalies? The true utility of this technique would mostly be in cases in which cardiac anomalies were not seen or were not the main anomaly discovered.

Reviewer #3:

This study was conducted to evaluate agreement between first trimester ultrasound findings of congenital heart disease and autopsy using histology slides in 3D imaging reconstruction. Although the study is small (n=6), the study demonstrates concordance between prenatal ultrasound and autopsy using 3D imaging reconstruction with histology slides.

General questions for authors:

Were the pathologists involved in the study subspecialized (i.e. pediatric or cardiovascular pathologists)?

It is not universally clear what imaging constitutes "first-trimester anomaly scan". Was the prenatal imaging, performed in this study, the basic cardiac screening exam as recommended by ISUOG Practice Guidelines or fetal echocardiogram or both?

Suggest manuscript be edited to follow format outlined by Obstetrics & Gynecology in Instructions for Authors.

"Histological virtuopsy" has been used multiple times throughout the manuscript. Virtuopsy is defined as a non-invasive autopsy. The histological slides used in 3D imaging to reconstruct the heart were obtained by traditional autopsy. Suggest changing "histological virtuopsy" to histological 3D imaging or histological 3D imaging reconstruction throughout the manuscript.

Specific comments:

Abstract

Objective:

Page 1, lines 4-6: Suggest changing sentence to: To evaluate the usefulness of three-dimensional (3D) reconstruction of histology slides to confirm congenital heart disease (CHD) detected by first trimester fetal cardiac ultrasound.

Manuscript

Introduction

Page 2, lines 53-55: Change "Imagistic" to Imaging at the beginning of the sentence. Also, please clarify the sentence. Have the other imaging methods been proposed as an audit for heart anomaly confirmation suspected by other imaging modalities (ultrasound)?

Page 3, line 56: Suggest changing stereomicroscopic autopsy to stereomicroscopic examination.

Conclusion

Page 23, line 415: Recommend changing first sentence to: We have shown that 3D histological imaging reconstruction of fetal hearts consistently confirm first trimester ultrasound imaging findings of congenital heart anomalies.

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Sincerely,

Torri D. Metz, MD, MS  
Deputy Editor, Obstetrics

The Editors of Obstetrics & Gynecology

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

Dear Dr. Torri,

We would like to thank you for time in reviewing our paper. Bellow you can find all of the editors and reviewer's comments bolded and out point by point answers.

#### **EDITOR COMMENTS:**

**1. Thank you for submitting this work to Obstetrics & Gynecology. If you elect to submit a revision for consideration, please format as a Procedures and Instruments article, and follow the author instructions for that type of submission, which will result in a reduction in word count.**

**\* <https://journals.lww.com/greenjournal/Pages/InformationforAuthors.aspx#II-H>**

Thank you for the editorial suggestions regarding the Procedures and Instruments article format. The article has been formatted accordingly. This resulted in a new word count of

**2. Please note the following:**

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

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We have rewritten the labels accordingly. A1-D1 are now A-D, A2-D2 are now E-H and lastly, E is now I, F is J and G is K.

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Figure 6 has been moved to supplemental digital content. It is now Appendix 1.

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Figure 7 has been moved to supplemental digital content. It is now Appendix 2.

**\* Figure 8: Please remove A-D labels, these will be added back per journal style. Note that we cannot break A-D into A1, A2, etc. Please upload as a figure file on Editorial Manager.**

Figure 8 is now Figure 6. The labels have been rewritten A1-C1 are now A-C, A2-C2 are now D-F and D-G are now G-J.

**\* Figure 9: Is this figure original to the manuscript? Permission may be required. Please upload as a figure file on Editorial Manager.**

Figure 9 is now Figure 7.

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Figure 10 has been moved to supplemental digital content. It is now Appendix 3.

**\* Figure 11: Please remove A-C labels, these will be added back per journal style. Note that we cannot break A-D into A1, A2, etc. Please upload as a figure file on Editorial Manager.**

Figure 11 has been moved to supplemental digital content. It is now Appendix 4. The label have been rewritten and now A1-C1 are D-F.

**\* Figure 12: Please remove A-B labels, these will be added back per journal style. Please upload as a figure file on Editorial Manager.**

Figure 12 is now Figure 8.

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Figure 13 is now Figure 9.

We mention that all of the figures are original to the manuscript. They have not been published anywhere nor taken from other articles or books. All of the figures and appenxies have been uploaded in the Editorial Manager, without any labels written on them.

## **REVIEWER COMMENTS:**

### **Reviewer #1:**

**#1. Thank you for a well written narrative about the meticulous reconstruction of abnormal embryonic human structures to confirm early imaging findings of cardiac anomalies. The precision of your methods and the resulting images and interpretation are nothing short of amazing. Please consider the following comments and questions.**

Reply #1. Thank you for your time in reviewing our paper and we appreciate your kind words.

**#2. What is the incidence of serious congenital heart defects among live births and under what circumstances might discovery of such abnormalities intrapartum lead to a decision to terminate the pregnancy? What options are available?**

Reply #2. CHD are the most common congenital abnormality, as they affect nearly 1% of the new-borns. Also, CHD represents a leading cause of infant mortality, because 18% of the affected new-borns die within the first year of life, which accounts for more than half of childhood deaths secondary to congenital

malformations. Cardiac malformations detection varies with expertise and, in general, they are among the abnormalities most frequently missed at the prenatal anomaly scan

Moreover, in a long-term infant mortality survey, World Health Organization reported that 42% of infant deaths were attributable to cardiac defects

The option to terminate a pregnancy when a fetal heart anomaly is detected is influenced by numerous factors. The parental factors include personal, religious or legal aspects that enables the couples with the option of pregnancy termination, when the fetus is affected by a severe condition. The medical factors refer to the ability of the health-care system to offer proper urgent medical assistance to new-borns with a heart malformation and the existence of a properly equipped medical center in the respective region to manage such diseases). An early detection of the malformative conditions should start with the first trimester, when the pregnancy can be terminated in case of severe abnormalities with lower medical, financial and emotional costs.

We added the following paragraphs:

„Congenital heart diseases (CHD) affect nearly 1% of new-born and represents a leading cause of infant mortality, as 18% of the affected new-borns die within the first year of life, which accounts for over half of childhood deaths secondary to congenital malformations<sup>1</sup>. Moreover, in a long-term infant mortality survey, World Health Organization reported that 42% of infant deaths were attributable to cardiac defects<sup>2</sup>.“ Lines 98-103 in the “Introduction”

and

“The option to terminate a pregnancy when a fetal heart anomaly is detected is influenced by numerous factors however first trimester termination implies lower medical, financial and emotional costs<sup>23,24</sup>” lines 332-334 in the “Discussions” part of the manuscript

### **#3. From a practical point of view how desirable would it be to have the ability to conduct your diagnostic confirmatory methodology available widely (regionally or globally)? Would the cost of such testing be a financial burden to the individuals involved?**

Reply #3. The need for a confirmation method is universal throughout the medical practice. Prenatal diagnosis should be audited / confirmed by the pathology gold-standard confirmation in cases of pregnancy termination or fetal demise and it should not be different in the first trimester. Therefore, each malformation, detected prenatally using ultrasound, should be subjected for confirmation if pregnancy termination is elected.

The protocol we propose implies general low costs, generic equipment and easily acquirable consumables / software and, furthermore, the learning curve of each step is not steep, as the much of the technique is widely used in general pathology practice. We do not consider such testing to be a financial burden nor time consuming, especially since other confirmation methods as the high-resolution magnetic resonance imaging and microfocus computed tomography require expensive and unavailable equipment and trained personnel.

We have added the following paragraph to the manuscript “Each malformation, detected prenatally using ultrasound, should be subjected for confirmation if pregnancy termination is elected. Given the high incidence of CHD, a reliable and widely available method should be implemented. The H3DIR protocol used in our study implies general low costs, generic equipment and easily acquirable consumables / software. Furthermore, the learning curve of each step is not steep, as the technique is widely used in general pathology practice. We do not consider such testing to be a financial burden nor time consuming, especially that the process can be automated, further reducing the time in preparing and scanning slides<sup>23</sup>.“ Lines 343-349 in the „Discussions” chapter.

### **#4. What are the clinical and public health implications of such confirmatory testing for the general public especially in countries with laws that limit or ban first trimester pregnancy termination except in certain circumstances?**

Reply #4. The method proposed by our study enables first trimester CHD pathological confirmation. This may have significant clinical and public health implications especially in countries with laws that limit or ban first trimester pregnancy termination except in certain circumstances as major anomalies detection,

because it will provide early prenatal diagnosis audit. Still, in any settings, regardless of the limitations, the 3D histological imaging reconstruction of fetal heart would enable a reliable diagnosis in fetal demise or spontaneous abortion cases.

**#5. Do you think because of the basic science importance of your efforts you would be best served by submitting your work to a specialty journal dealing more with clinical pathology, clinical imaging, cardiology, or human embryology?**

Reply #5. We acknowledge the interdisciplinary nature of the article as it implies the work of several medical specialties. However, the concept of this study was developed by specialists in maternal-fetal medicine, thus the desire to publish the article in an Obstetrics and Gynecology journal.

Our previous research on this subject has been already published in an embryology and pathology journal that is cited in the present manuscript.

We believe that the potential of our technique should be acknowledged by all the professionals involved in the field, especially the ones that deliver the prenatal diagnosis. Given the fact that the ob-gyn doctors or midwives usually perform fetal anomaly scan depending on the regional settings, we aim for a dissemination in our medical specialty journals.

#### **Reviewer#2:**

**In the manuscript under review, we evaluate the results of a case series evaluating the use of three-dimensional reconstruction of histology slides following first-trimester termination for suspected congenital heart defects. The authors had 6 cases in which this novel technique allowed them to detect minor anomalies not previously seen.**

**A few comments on the manuscript are as follows:**

#### **ABSTRACT**

##### **1. No major issues were noted**

Reply #1. We thank the reviewer for the time spent to evaluate our study design and results.

#### **INTRODUCTION**

##### **2. No clear hypothesis is stated by the authors**

Reply #2: The present research aims to evaluate this method's feasibility in identifying fetal heart anomalies detected prenatally at the first trimester anomaly scan. The hypothesis of our study is that first-trimester fetal heart three-dimensional (3D) reconstruction of serial histological slides is able to confirm fetal heart abnormalities.

We modified the manuscript accordingly (Introduction, lines 71-73): "The hypothesis of the present research is that this technique is useful in identifying fetal heart anomalies detected prenatally at the first trimester anomaly scan."

#### **METHODS**

##### **3. Line 66-71 - at what gestational age were these ultrasound examinations done?**

Reply #3. The ultrasound examinations were performed between 12+1 weeks – 13+6 weeks of gestation. We added "at the gestational age of 12+1 – 13+6 gestational weeks", lines 82-83, for clarification.

#### **RESULTS**



**4. Line 143 - why was an isolated VSD during the first trimester considered an anomaly? Most of these close on their own**

Reply #4: It is correct that isolated VSD detected in the first trimester should not influence the pregnancy management. However, in our case, the fetus associated Turner syndrome which led to pregnancy termination. Therefore, we took advantage of this situation to investigate if small defects suspected by first trimester ultrasound scan can be confirmed by histological 3D reconstruction.

We modified the manuscript accordingly: "Figure 2. Duplex gray-scale and color Doppler cardiac sweep in 12 weeks +3 days fetus, showing a ventricular septal defect in a fetus detected with Turner syndrome." (Lines 164-165)

**DISCUSSION**

**5. As an overall comment, do the authors have any data on this technique in cases of first-trimester autopsy not related to cardiac anomalies? The true utility of this technique would mostly be in cases in which cardiac anomalies were not seen or were not the main anomaly discovered.**

Reply #5. In our center we use this technique whenever necessary to confirm first trimester fetal structures or anomalies, not necessarily related to fetal heart. The authors have previously published several papers regarding the implications of first-trimester autopsy complemented by histological evaluation:

- Șorop-Florea M, Ciurea RN, Ioana M, Stepan AE, Stoica GA, Tănase F, Comănescu MC, Novac MB, Drăgan I, Pătru CL, Drăgușin RC, Zorilă GL, Cărbunaru OM, Oprescu ND, Ceașu I, Vlădăreanu S, Tudorache Ș, Iliescu DG. The importance of perinatal autopsy. Review of the literature and series of cases. Rom J Morphol Embryol. 2017;58(2):323-337.
- Iliescu D, Comănescu A, Antsaklis P, Tudorache S, Ghiluși M, Comănescu V, Paulescu D, Ceașu I, Antsaklis A, Novac L, Cernea N. Neuroimaging parameters in early open spina bifida detection. Further benefit in first trimester screening? Rom J Morphol Embryol. 2011;52(3):809-17.
- Nagy RD, Ruican D, Zorilă GL, Istrate-Ofițeru AM, Badiu AM, Iliescu DG. Feasibility of Fetal Portal Venous System Ultrasound Assessment at the FT Anomaly Scan. Diagnostics (Basel). 2022 Jan 31;12(2):361.

We add a mention of this (lines 455-463): "H3DIR also provides an opportunity to retain specific slices for supplementary special stains, which can aid in evaluating the fetal heart<sup>41</sup> or add valuable information to standard autopsy<sup>27,42,43"</sup>

**Reviewer #3:**

**#1. This study was conducted to evaluate agreement between first trimester ultrasound findings of congenital heart disease and autopsy using histology slides in 3D imaging reconstruction. Although the study is small (n=6), the study demonstrates concordance between prenatal ultrasound and autopsy using 3D imaging reconstruction with histology slides.**

**General questions for authors:**

**Were the pathologists involved in the study subspecialized (i.e. pediatric or cardiovascular pathologists)?**

Reply #1. We thank the reviewer for his / her's general appreciations. In Romania we do not have perinatal or cardiovascular pathology subspecialties. However, only some of the pathologists perform fetal autopsy, depending on their experience in the field. Of course, in our study the best professionals of our center were involved, working together with maternal-fetal specialists.

**#2. It is not universally clear what imaging constitutes "first-trimester anomaly scan". Was**

**the prenatal imaging, performed in this study, the basic cardiac screening exam as recommended by ISUOG Practice Guidelines or fetal echocardiogram or both?**

Reply #2: Fetal echocardiogram was performed on all of the fetuses included in the study, however the ultrasound examination was not limited to the fetal heart. Each fetus was subjected to a detailed anatomical scan for a complete evaluation, following a scanning protocol designed, implemented and previously published by our center. For the same purpose we added a citation to underline the need of using color Doppler during the first trimester fetal heart evaluation.

We modified accordingly the Methods section that now reads (lines 81-86): "Prior to termination, a detailed ultrasound examination was performed by a team of experienced fetal-maternal medicine specialists using transabdominal ultrasonography at the gestational age of 12-13 weeks, following the already published protocol<sup>6</sup>, using colour or high-definition directional power Doppler<sup>22</sup>. Transvaginal approach was used when fetal or maternal conditions were unfavourable."

**#3. Suggest manuscript be edited to follow format outlined by Obstetrics & Gynecology in Instructions for Authors.**

Reply #3. Thank you for your suggestion. The manuscript has been edited accordingly.

**#4. " Histological virtuopsy" has been used multiple times throughout the manuscript. Virtopsy is a defined as a non-invasive autopsy. The histological slides used in 3D imaging to reconstruct the heart were obtained by traditional autopsy. Suggest changing "histological virtuopsy" to histological 3D imaging or histological 3D imaging reconstruction throughout the manuscript.**

Reply #4. Thank you for your suggestion. We have changed the manuscript accordingly.

We added an abbreviation to histological 3D imaging reconstruction: H3DIR.

Line 305-306: changed "histological virtuopsy" to "H3DIR"

Line 337: changed "histological virtuopsy" to "H3DIR"

Line 395: changed "histological virtuopsy" to "H3DIR"

Line 400: deleted "as the best virtuopsy approach"

#### **Specific comments:**

#### **#5. Abstract**

##### **Objective:**

**Page 1, lines 4-6: Suggest changing sentence to: To evaluate the usefulness of three-dimensional (3D) reconstruction of histology slides to confirm congenital heart disease (CHD) detected by first trimester fetal cardiac ultrasound.**

Reply #5. We thank the reviewer for the suggestion. We modified the manuscript accordingly - lines 4-6.

#### **#6. Manuscript**

##### **Introduction**

**Page 2, lines 53-55: Change "Imagistic" to Imaging at the beginning of the sentence. Also, please clarify the sentence. Have the other imaging methods been proposed as an audit for heart anomaly confirmation suspected by other imaging modalities (ultrasound)?**

Reply #6. We changed "Imagistic" to "Imaging" - line 61.

We clarified this sentence to reflect the purpose of each imaging investigation: "Imaging methods such as 9,4-T magnetic resonance imaging (MRI) and microcomputed tomography (Micro-CT)[2-4] have been proposed as an audit for confirmation of fetal heart anomalies detected prenatally by US.". - lines 61-63

**#7. Page 3, line 56: Suggest changing stereomicroscopic autopsy to stereomicroscopic examination.**

Reply #7. We agree the reviewer suggestion. We changed "*autopsy*" to "*examination*" - line 64-65. We also added "*conventional*" autopsy to clarify the type of autopsy performed - line 65.

**#8. Conclusion**

**Page 23, line 415: Recommend changing first sentence to: We have shown that 3D histological imaging reconstruction of fetal hearts consistently confirm first trimester ultrasound imaging findings of congenital heart anomalies.**

Reply #8: We agree the reviewer opinion. We changed the manuscript accordingly – lines 434-436.

Best regards,

Dan Ruican, MD