1. **PROTOCOL TITLE:** Improved diagnosis of placental lesions via special and immunostains

2. **VERSION DATE:** 1.02, 06/24/2020
3. **NU RESEARCH TEAM**

PRINCIPAL INVESTIGATOR:
Jeffery A. Goldstein, MD, PhD
Department of Pathology

CO-INVESTIGATOR:
Elisheva D. Shanes, MD
Department of Pathology

4. STUDY PURPOSE:

The placenta is the first organ to form and acts as the fetal lungs, gut, kidney, and skin. Abnormalities in the placenta are identified in or causative of many problems of pregnancy and may have life-long consequences[1,2]. Over 150 different abnormalities in the placenta are described, most of which are diagnosed using only macroscopic examination and routine histology with hematoxylin and eosin (H&E) [3,4]. However, we have found in practice that some lesions cannot be clearly diagnosed, particularly between villous infarction (hereafter: infarct) and perivillous fibrin deposition (hereafter: fibrin) and between intervillous thrombus (hereafter: thrombus) and infarction-thrombus due to abruption (hereafter: abruption)

The purpose of this study is to show that some lesions show different patterns of staining with special and immunohistochemical stains and that those patterns can be used in difficult cases. The audience is primarily practicing pathologists who may be aided in diagnosing difficult cases.

5. INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:
- Patients delivering at Northwestern Memorial Hospital with placentas submitted for examination 1/1/2007 – 6/1/2020
- Diagnosis of infarct or fibrin or description of a lesion with features intermediate between infarct and fibrin or where a differential diagnosis is given that includes both infarct and fibrin.

  OR
- Diagnosis of thrombus or abruption or description of a lesion with features intermediate between thrombus and abruption or where a differential diagnosis is given that includes both infarct and fibrin.

Exclusion criteria:
- None.
- We are aware of at least 1 male patient delivering at our hospital, therefore we will not exclude patients on the basis of sex.

- Diseases of pregnancy are more common at extremes of age and inclusion of pediatric patients is encouraged by NIH, therefore we will not exclude patients on the basis of age.

6. PROCEDURES INVOLVED

Study type: Indicate if this study is 1) retrospective; 2) prospective; or 3) BOTH retrospective and prospective.
NOTE: if you plan to collect biospecimens prospectively solely for research purposes as part of this study (e.g., through biopsies), then you cannot use this template.

☒ **Retrospective Review** (the data and/or specimens already exist at the time this study is submitted for initial IRB review)
Date Range of data/specimens to be reviewed: 1/1/2007 – 6/1/2020

☐ **Prospective Review** (the data and/or specimens do not exist when this study is submitted to the IRB for initial review – for specimens, you can use this template only if the specimens are being collected for non-research purposes such as medical treatment/diagnosis)

☐ **BOTH Retrospective and Prospective Review**
Date Range of data/specimens to be reviewed:

7. CHARACTERISTICS OF DATA/SPECIMENS TO BE ANALYZED

We will perform a retrospective review of NMH records kept from 2007 through May 2020 of patients delivering at NMH with a diagnosis of villous infarction, increased perivillous fibrin deposition, intervillous thrombus, features of abruption, or indeterminate lesions for which the differential diagnosis includes two or more of the above lesions. Accesssion numbers and pathologic data will be manually extracted from pathology reports in the laboratory information system. Patient chart information (e.g. from EPIC or electronic data warehouse) will not be collected.

Prior existing placenta specimens will be analyzed for this study. Stored tissue blocks will be requested from the pathology repository using the accession number. They will be de-identified by removing patient identifiers and replacing them with a unique study ID number. Deidentified blocks will be submitted to the NU pathology core facility (https://www.feinberg.northwestern.edu/research/cores/units/pathology.html), an institutional resource that performs experiments for investigators lacking lab space or expertise. Tissue blocks will be returned to their original storage location immediately after stains are performed by the core facility (estimated ~1 monthe depending on queue + technical difficulties). Duration of storage is determined by the rules and regulations of the Pathology laboratory for clinical purposes.

For a list of data elements collected, please see APPENDIX A: DATA COLLECTION DOCUMENT. Medical record numbers, date of birth, or patient names will not be

collected. Data for this study have not been collected in a previous research study and use of data does not require any special permissions, restrictions, and/or agreements.

Proposed sample size for this study is 60 patients consisting of 10 patients with each of the 4 lesions and 20 patients with lesions where the differential diagnosis includes at least 2 of the lesions.

The data will be analyzed by the research team using statistical software. Presence and degree of staining will be categorized qualitatively and quantitatively. Descriptive statistics of variables analyzed will be expressed as mean for quantitative variables and frequency (%) for categorical variables. Student's t-test, chi-squared test, or Mann-Whitney U test will be used for data analysis depending on whether variables are categorical or quantitative and parametric or non-parametric.

8. ACCESS, SECURITY, AND MANAGEMENT

The only direct identifiers that will be recorded are the study subject's surgical pathology specimen accession number from the laboratory information system. No names will be recorded. This identifier will constitute the key to a de-identified dataset. Each study subject will be assigned a unique study ID number. The key to the code will be recorded in the Coded Identifier List in a password-protected Excel spreadsheet stored on the PI and co-investigator(s)' password-protected computer in a locked office in the Pathology Department at NMH. Only the PI and co-investigator(s) have access to the key to the code. De-identified dataset will be stored in a password-protected Excel spreadsheet stored in a dedicated project folder in the PI's FSM-files server. The research team will have access to the de-identified dataset. The key to the code and de-identified dataset will be stored for a minimum of three years after study completion. After this retention period has passed and the data is no longer needed, documents will be destroyed by permanently deleting them.

For additional information on access, security, and management, please see our Data Security Plan attached to this protocol.

9. POTENTIAL RISKS

The largest risk is accidental release of patient data. This is a risk in all studies and will be minimized as described in the data safety plan. Risks will be minimized by storing patient identifiers on a password-protected computer in a locked, badge-secured space. Identifiable data will not be placed on non-secured computers, mobile devices, portable storage, or laptops.

10. POTENTIAL BENEFITS OF THIS PROJECT

The study is unlikely to directly benefit participants. This study may improve diagnosis of placental abnormalities. Some lesions (infarct, abruption) carry a risk of cerebral palsy in the infant and risk of recurrence in future pregnancy. Fibrin may represent Massive

Perivillous Fibrin Deposition, which has a high risk of recurrence in future pregnancies and can be prevented in some patients with treatment. Whenever appropriate, subjects will be provided with additional pertinent information after participation.

11. INFORMED CONSENT AND WAIVER OF CONSENT

We are requesting waiver of consent because: This research involves no more than minimal risk to the subjects as patients will not undergo any procedures. The waiver or alteration will not adversely affect the rights and welfare of the individuals whose data is being analyzed. The research could not practicably be carried out without a waiver of consent because cases of interest may have occurred long before this study and many patients will no longer be reachable. Identification of cases and requisitioning material requires the use of the pathology accession number, however this will be de-identified as soon as practicable.

12. HIPAA AUTHORIZATION AND WAIVER OF AUTHORIZATION

We are requesting waiver of HIPAA authorization.

- This PHI is necessary to conduct a study of existing clinical biospecimens
- The PHI involves no more than minimal risk
  - Pathology accession numbers will only be accessible by the PI
  - Data (including location and date PHI) will be stored on secured computer. No data will be on physical, lose-able media.
- The PHI will not be be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information for which an authorization or opportunity to agree or object is not required by 45 CFR 164.512.
- This research cannot be practicably be conducted without waiver for the reasons given for waiver of consent.

APPENDIX A: DATA COLLECTION DOCUMENT

The majority of data will include review of glass slides and pathology reports. The specimens were previously collected and reports were previously generated for patient care and no additional specimens will be collected. Medical record numbers, date of birth, or patient names will not be collected.

Pathology data elements (collected manually from the laboratory information system):

- Pathology accession number
- Macroscopic description.
- Histopathologic description
- Diagnosis and any differential diagnosis given
- Immunohistochemistry data