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National Association of Medical Examiners Position Paper: **Recommendations for the Investigation of Maternal Deaths**

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Abstract

Maternal mortality is a metric used by nations to assess the overall well-being of their citizens. Accurate measures of maternal death including both pregnancy-related and pregnancy-associated deaths and their causes are crucial to understanding the health of a population. In their public health role, the forensic pathologist/medical examiner/coroner (ME/C) has the ability to gather and provide this vital information. The National Association of Medical Examiners (NAME) convened a panel of forensic pathologists and other experts in the field of maternal mortality to create a position paper regarding the investigation, autopsy, and certification of pregnancy-related and pregnancy-associated deaths, to discuss common causes of these deaths, and to discuss the vital interplay between the ME/C and other related entities in reviewing these deaths to improve public health. This position paper is advisory and supplemental to the NAME Forensic Autopsy Standards.

Positions

-Jurisdiction: Jurisdiction is dictated by legal statute; however, pregnancy-related and pregnancy-associated (death during or within one year of pregnancy) are unusual and unexpected and therefore already fall within the realm of reportable deaths to the ME/C in nearly all states [1]. It is recommended that ME/C offices consider adding maternal deaths to their published lists of reportable deaths.

-Reporting and Case Disposition: Ideally all pregnancy-associated and pregnancy-related deaths would be reported to the ME/C with a low threshold for accepting jurisdiction and performing an autopsy. This aligns with the NAME Autopsy Standard A2.3 “the forensic

pathologist or representative shall investigate all unexpected or unexplained deaths of those in apparent good health" [2].

-Examination: Maternal deaths are often unexpected, unusual, and concerning and therefore deserve thorough review which may include a full autopsy. This aligns with NAME Autopsy Standard B1.12 "autopsies shall be performed when the forensic pathologist deems a forensic autopsy is necessary to determine cause or manner, document injuries/disease, collect evidence, or adequately document findings and issues of concern" [2].

-Autopsy Techniques and Ancillary Studies: Recommendations for the examination of decedents accepted for autopsy are provided in this paper for informational and educational purposes to support any pathologist who performs these examinations.

-Public Health Participation: ME/C cooperation with local public health departments and participation on maternal mortality review committees (MMRCs) to share and evaluate maternal mortality data is crucial. The ME/C should advocate to be included in their jurisdictional MMRC.

-Pregnancy Data: Obtaining and documenting pregnancy status within the past year for all decedents of childbearing age/potential is of vital importance. When utilized properly, the pregnancy checkbox on the death certificate provides essential public health information that is critical to the accuracy of maternal mortality data.

-Death Certification: The National Center for Health Statistics has published recommendations for the certification of pregnancy-associated and pregnancy-related deaths [3].

Intro/Background

Maternal deaths are an important yet often under-investigated aspect of forensic pathology. Maternal deaths also represent a significant public health concern, with wide-reaching implications for families, communities, and healthcare systems. Globally, the World Health Organization (WHO) estimates that 287,000 women die during pregnancy or childbirth every year, and the vast majority of these deaths are preventable [4].

The WHO defines a maternal death as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes." Late maternal deaths are those that occur from 43 days

to 1 year after pregnancy [5]. These definitions capture what the Center for Disease Control (CDC) classifies as so-called pregnancy-related deaths but fail to recognize the important category of pregnancy-associated deaths – that is, maternal deaths that are physiologically unrelated to the pregnancy and occur within 1 year of the pregnancy's end [6]. Pregnancy-associated deaths include suicidal, homicidal, and accidental injuries involving pregnant and postpartum persons, and are a leading cause of maternal death in the United States (US). Useful definitions are summarized in Table A.

The US has one of the highest maternal mortality rates among high-income countries. In 2023, the US had a maternal mortality rate (MMR) of 18.6 deaths per 100,000 live births, which is significantly higher than other high-income nations such as Canada (11 deaths per 100,000 live births), Germany (4 deaths per 100,000 live births), and the United Kingdom (10 deaths per 100,000 live births) [4, 7]. Within the US, large disparities are created by racial and socioeconomic inequities. Black women in the US are at least two and a half times more likely to die from pregnancy-related complications than White women, a disparity driven by factors such as systemic racism, lack of access to quality healthcare, environmental stressors, a higher prevalence of chronic medical conditions, and differences in various social determinants of health such as income and education [7, 8].

In recent years, additional factors have affected the maternal mortality rate in the US and abroad. A sharp uptick in the MMR was seen during the early years of the COVID-19 pandemic, with rates increasing from 20.1 in 2019 to 32.2 in 2021 [9]. In the years 2020 and 2021, COVID-19 contributed to one quarter of all maternal deaths, and disparities among racial and ethnic groups continued or worsened [10]. The so-called 'opioid epidemic' can also be blamed for a persistent and increasing number of maternal deaths. In many states across the nation, pregnancy-associated deaths due to drug intoxication are a leading cause of maternal mortality [11, 12]. Other research has postulated that a trend towards delayed childbearing plays a role, with many studies demonstrating that increasing maternal age is a demographic risk factor for maternal mortality [13].

Accurate data are critical to the study of any public health matter, and maternal deaths are no exception. The gathering of precise maternal mortality statistics has long been complicated by issues such as under-reporting, misclassification, and the lack of consistent definitions and reporting standards [14, 15] . Medical examiners and coroners (ME/C) are uniquely positioned to help by virtue of their expertise and meticulous data collection practices.

In the sections that follow, guidelines for jurisdiction, recommendations for investigation and autopsy, common causes of maternal death, guidelines for death certification, the importance and role of the maternal mortality review committee (MMRC), and areas in

which additional research or advocacy is needed are highlighted. Overall, the recommended position is that more maternal deaths require ME/C investigations that are standardized, comprehensive, and focused on the delivery of quality information about the cause of death. Multidisciplinary collaboration can be extremely valuable.

The role of the ME/C extends beyond determining cause and manner of death; it involves contributing to a broader understanding of the root causes of mortality, informing public health interventions, and improving the standard of care [16]. Ultimately, an enhanced and more standardized approach to investigating maternal deaths will not only save lives but also provide valuable data for policy reform aimed at eliminating preventable maternal mortality.

Guidelines for Jurisdiction

ME/C offices operate in the arena of sudden and unexpected deaths. Maternal deaths frequently fall into this subset given the general health and younger age of these decedents. Pregnancy-associated deaths from suspected or apparent physical injury or drug use normally fall into the jurisdiction of the ME/C and are evaluated to determine the cause and manner of death. Pregnancy-related deaths often present as sudden or unexpected deaths without a clear etiology and therefore warrant an investigation by the ME/C [17]. These deaths may occur outside a medical facility or during a hospitalization before an underlying etiology can be established with reasonable certainty. Other pregnancy-related deaths may occur following a well-documented hospital course with a clear link between the pregnancy complication and the death.

In some jurisdictions, legislation or local agreements with health departments may require deaths of women within one year of pregnancy be reported to and/or investigated by the ME/C [18]. In other jurisdictions, there may be no specific requirement, and the decision to investigate pregnancy-related and pregnancy-associated deaths without a known etiology is based solely on subjective interpretation of the sudden and unexpected nature of the death.

An important group of potential pregnancy-related deaths which may not be routinely reported to and/or investigated by the ME/C offices as an accepted and standard practice are those deaths which occur in a health care setting, such as a hospital or birthing center, especially those occurring during pregnancy, labor, delivery, or the postpartum period (42 days after the end of a pregnancy). If such a death is not reported, or if it is reported and jurisdiction is declined because of medical attendance and/or willingness of a clinical

physician to certify the death, a ME/C investigation (with autopsy as appropriate) will not likely occur. The development and implementation of systems to facilitate timely reporting and identification of these potential pregnancy-related or pregnancy-associated deaths would increase the numbers of potential deaths which are optimally evaluated, improving the quality and consistency of maternal death investigation.

While a systematic survey of ME/C jurisdictions has not been completed, there are current systems designed to enhance timely reporting of these deaths including New York City's non-legislative requirement to report them [19] and Washington state's law requiring hospitals and licensed birth centers to make a reasonable and good faith effort to report all deaths that occur during pregnancy or within forty-two days of the end of pregnancy to the local ME/C within 36 hours of death [18]. Professional organizations for ME/Cs could encourage the development and implementation of enhanced reporting systems, in conjunction with increased funding and resources to support these investigations.

An autopsy may not be necessary in deaths with a well-established cause, such as terminal malignancy, but an autopsy may provide a more accurate cause of death in other cases with less clinical certainty. The autopsy diagnosis has been shown to differ from the clinical diagnosis in 9.9% to 36% of maternal deaths with autopsy [20, 21], with pulmonary thromboemboli being the most common clinical diagnosis disproven at autopsy in one study [22]. In another study, the underlying cause of 38% of maternal deaths without autopsy could not be determined based on the clinical record alone [20]. Though many pregnancy-related and pregnancy-associated deaths without a specific etiology in the year after pregnancy will present with a suspected natural manner of death, an ME/C investigation is recommended to facilitate an accurate determination of the underlying cause of death, preferably with an autopsy, and answer questions that serve the greater public health concern around the observed trend of increasing maternal deaths.

Recommendations for Investigation and Autopsy

Investigative Information Specific to Pregnancy-Associated / Related Deaths

A medicolegal death investigation of maternal deaths involves a detailed process to determine the cause of death, the manner of death, and to identify causative or contributing factors to the death. These investigations are crucial for understanding the underlying factors contributing to the death and for preventing future deaths. It is important for medicolegal death investigators to ask about the pregnancy status of female decedents, especially those who are of reproductive age. This question is essential

because it aids in identifying probable maternal deaths and promoting accuracy in maternal mortality statistics [23].

A thorough review of the woman's medical history, prenatal care, and delivery notes is essential in identifying potential risk factors or complications that may have contributed to the death. If the death happens outside of a healthcare setting, investigators may visit the scene (e.g., at home) to gather information about the circumstances surrounding the death and those that might have contributed to the death. When the death occurs in a healthcare setting, investigators will review hospital records, including medical charts, delivery records, and the timing of interventions. Accurate and thorough documentation of all findings is essential. Recommended screening questions are included in Table B.

Medical Records Specifically Related to Maternal Autopsy

In addition to standard practices related to record review, the following records have been shown to be helpful:

- Obstetric related medical records from the delivery facility, hospitalizations before and after delivery, and from the prenatal and postnatal obstetric providers.
- Prenatal and antemortem lab data (especially microbiologic, coagulation and hematologic information).
- Names and contact information for all primary obstetric (including prenatal) and hospital providers.

Autopsy Findings Suggestive of Early Pregnancy

Because the possibility of a pregnancy-related or pregnancy-associated cause of death should be considered in the evaluation of any unexpected death of a woman of reproductive age (10 to 50 years old), the autopsy of any female decedent often includes external and internal evaluation of the female genitalia, including internal examination of the uterus and cervix and bisection of the ovaries. There are anatomic findings observable at autopsy which may be suggestive of early pregnancy, and therefore warrant additional tests for confirmation. Confirmatory tests may include histologic evaluation of the uterus, sampling of "products of conception" for possible later testing for paternity, and/or sampling of maternal urine/blood for possible pregnancy testing (see below). Anatomic features of early pregnancy can include:

- Enlarged uterus, sometimes with a "boggy" consistency.
- Enlarged edematous ovaries with presence of a corpus luteum.

- Thickened endometrium, even in the absence of a macroscopically identifiable gestational sac [24].

Postmortem Pregnancy Testing

As mentioned above, early pregnancy can be subtle and therefore difficult to diagnose, particularly if there is no known history of possible pregnancy. Early research has shown that postmortem pregnancy testing can be performed not only on urine, as is done in living women, but also using other bodily fluids such as vitreous fluid [25]. The results of this testing may inform decisions about the pregnancy checkbox on the death certificate and provide additional information about the cause and manner of death, particularly if the death is unnatural (i.e. a homicide or suicide) (see further discussion below).

Pregnancy-Associated Deaths

Pregnancy-associated deaths which occur as a result of injury or drug intoxication generally fall under the jurisdiction of the ME/C, with the cause of death identified using the usual jurisdictional procedures, which may include an autopsy. The pregnancy and the fetus are best evaluated and documented using standard procedures. Any examination and documentation of the fetus or infant may utilize guidelines described in the NAME position paper on the investigation and certification of fetal demise, stillborn, and early neonatal deaths [26], and the documentation of the pregnancy-related pathology can be done using the relevant sections of the guidelines described below for possible pregnancy-related or pregnancy-associated deaths.

GUIDELINES FOR AUTOPSIES PERFORMED IN THE SETTING OF MATERNAL DEATH

1. NAME Autopsy Standards and Applicable Position Papers

All autopsies should be performed in compliance with the NAME Autopsy Standards [27], and any relevant NAME Position Papers (such as those pertaining to deaths due to drug intoxication, epilepsy (SUDEP), investigation and certification of fetal demise, stillborn, and early neonatal deaths, genetic testing, etc.) [26, 28-30]. The recommendations here focus on elements of autopsy particularly relevant to possible pregnancy-related or pregnancy-associated deaths and can be used in conjunction with jurisdictional procedures and the NAME standards. Some of these techniques are highly specialized and are performed at the discretion of the prosector.

2. Facilities and Resources

At a minimum, autopsies for maternal deaths require good mortuary and laboratory facilities, including access to all necessary testing and storage. Additionally, the ME/C is encouraged to develop academic relationships with other clinical and pathology specialists who can be consulted in the interpretation of findings, as needed.

3. Pre-autopsy Consultation with Involved Clinicians

Depending on the circumstances of the death, pre-autopsy consultation with the involved clinical providers may be helpful, especially conversations with the primary obstetrician or delivering provider or other involved clinicians. Such discussions may identify the major clinical concerns and/or differential diagnoses, and/or provide insights related to procedural, anesthetic, or other factors relevant to the death.

4. The Autopsy

i. General Comments

The procedures described in this document are focused specifically on issues related to possible pregnancy-related or pregnancy-associated deaths.

When possible performing a complete autopsy is optimal.

Evidence collection, sampling for toxicology and other testing, and other standard autopsy procedures may be included as appropriate per the usual jurisdictional procedures.

All of the procedures and findings are then documented in the autopsy report. If applicable, in the report include a description of whether the fetus from the gravid uterus was returned to the mother's body after examination or kept separate.

ii. Photographs: In addition to external overall photographs, photographs of external and internal abnormalities, major pathologic findings, and evidence of injury and medical therapy, consider the following:

- External genitalia, including abnormalities and injuries.
- Internal in-situ organs, prior to removal of organs, especially the pelvic organs.

- Pelvic organs after removal, and to document the internal examination of the uterus and other relevant features.
- Gravid uterus, external and internal documentation.
- All separately received specimens (i.e. hysterectomy specimen, placenta, fetus).

iii. Postmortem Imaging:

If available, postmortem imaging (plain film radiographs, PMCT, etc) can be utilized based on jurisdictional procedures. This imaging can provide useful information about a potential cause of death (e.g. an air embolism). That being said, in most maternal deaths (both possible pregnancy-related or pregnancy-associated), postmortem imaging is not sufficient for the accurate determination of cause and manner of death, and a complete autopsy with histologic evaluation is necessary [31].

iv. External and Internal Examination Specific to Maternal Death

External Examination--General

- External genitalia, overall and abnormalities.
- Surgical incisions: Examine for evidence of infection and consider microbiologic evaluation as appropriate (see below).
- Measure general height of the uterine fundus.

Internal Examination— Examination of the Gravid Uterus at Autopsy

Examination of the gravid uterus and placenta may vary depending on individual features of the case. In general, in-situ examination will be followed by en bloc removal of pelvic organs, to include the unopened uterus and attached pelvic blood vessels, ideally including fallopian tubes and ovaries, and attached intact cervix.

-In-situ examination of uterus, fallopian tubes and ovaries: Document lacerations, surgical incisions, or areas of bulging, thinning, or external extension of the placenta through the uterine serosa.

-For obstetric trauma, consider retaining the female genital tract en bloc with the vasculature, bladder and rectum [31].

–If the cervix cannot be removed with the uterus, remove the uterus and cervix separately, incising as low as possible in the pelvis. The cervix can be separately evaluated, focusing on abnormalities such as adherence of placental tissue to the internal surfaces, and assessment for placenta accreta spectrum.

Opening the uterus is generally done after removal from the body. The unique features of a maternal death and autopsy can influence how the uterus is opened and further examined. This can be modified depending on clinical records describing antemortem imaging of the placenta and fetus, clinical history related to the pregnancy (for example, history of placenta previa or adherent placenta), delivery information including method of delivery, and external examination of the uterus for identification of abnormalities or incisions.

In general, the uterus is opened to avoid the fetus, and if possible, the placenta. In most cases, the placenta will be either in the anterior or posterior uterine body, and the uterus will be optimally opened with bilateral incisions through the cervix ("bi-valved") to create anterior and posterior halves, with modification based on clinical or pathologic findings.

Prior to and after opening the amniotic sac, photograph and document the in-situ position of the fetus, placenta, umbilical cord and other relevant details. Transect the umbilical cord and remove the fetus. Management of the fetus in the setting of a maternal autopsy depends on the circumstances of the case, but at minimum, an external examination of the fetus is recommended as described below.

Separately document findings of the internal uterus including any retained placental tissue if delivery has occurred. If the placenta or remnants are still present, do not remove them. Document the placental shape and estimated size, position with respect to the cervical os, umbilical insertion site on the placenta, and length of the umbilical cord if present. If feasible, fixation of the bi-valved uterus can optimize the examination and histologic sampling. Serial sectioning of the uterus and attached placenta allows assessment of placental and uterine thickness, and documentation of abnormalities, including placenta previa, placenta accreta spectrum, retroplacental hemorrhage (as in placental abruption), or evidence of infection.

<u>Internal Examination - Specific Circumstances (Also See Histology Section Below):</u>

Air embolism: If this is a consideration, use standard procedures as described in the literature (skull opened prior to thoracoabdominal incisions, observation of cerebral vessels in-situ for air bubbles, heart (right ventricle) incised / opened under water contained in pericardial sac to allow observation for air bubbles). Postmortem imaging may be useful if air embolism is a diagnostic concern.

Thromboembolism: Attempt to identify the source if possible, including pelvic and periuterine veins in pregnancy and postpartum setting. The parametrial vessels can be inspected for macroscopic evidence of embolic material. Deep veins of the legs can be examined for thrombosis.

Evidence of hemorrhage/pooled blood: Document quantity of blood or fluids in body cavities, and try to identify the source of bleeding (ruptured ectopic pregnancy, ruptured uterus, aneurysm, etc). Of note, pay close attention to the splenic vasculature prior to the removal of the organs as splenic artery aneurysms may otherwise be missed.

Obstetric injury (usually iatrogenic): Photograph in situ and identify the site of injury if possible.

Areas of infection: Photographic documentation followed by sampling for microbiologic and histologic evaluation (see histology).

Heart: Examination per standard procedures, including coronary arteries, valves, and a trimmed heart weight (important for evaluation of cardiomyopathy).

v. Additional Histology for Maternal Autopsies

Histologic evaluation will generally be more extensive than the usual ME/C autopsies. The amount of retained tissue may also be more extensive than usual, in that small tissue samples from most organs and tissues can be fixed in 10% buffered formalin for possible later histologic evaluation ("histology stock".)

Samples for Histologic Evaluation That Have Been Shown to be Helpful (see Tables C and D):

Heart and coronary arteries: at least one full thickness section of each cardiac ventricle

Lungs: one or two sections from each lung lobe

Kidney, liver, spleen, adrenals

Brain with leptomeninges

Pituitary (complete)

Internal genitalia:

-Cervix (including ecto and endocervix), bilateral ovaries, fallopian tube if abnormal

-Non-gravid uterus: several full thickness sections (endomyometrium)

-Gravid uterus: at least one representative full-thickness section of the uterus without placenta with the location specified (including decidua, myometrium, and serosa), section of uterus with placental attachment, representative central and peripheral sections of the placental disc, two samples of the umbilical cord (including one near the placental disc attachment), sections of free membrane roll, representative sections of placental abnormalities (abnormal attachment, previa, retained placenta, placental parenchymal abnormalities), representative sections of uterine abnormalities, and representative sections of bilateral parametrial vessels. For complex cases, consideration could be given to fixation and retention of the specimen for consultation with a pathologist with expertise in perinatal, obstetric, and/or placental pathology.

Histologic Sampling for Specific Situations:

Area of infection: Histologic sampling of endomyometrial tissue or soft tissue in necrotizing soft tissue infection can be diagnostic of cause of death and microbiologic etiology.

Suspected amniotic fluid embolism (AFE): Parametrial vessels (bilateral ideal), additional lung sections, and specific stains to facilitate identification of amniotic fluid components may be useful (e.g. Attwood's stain, high-molecular weight cytokeratin immunostaining; also see discussion of amniotic fluid embolism below) [31].

Suspected injury (cervical, vaginal, uterine), which is usually iatrogenic but can also occur with traumatic injury: Sample areas of injury, as disrupted vessels may be identified histologically.

Ectopic pregnancy: Uterus, ovaries, and ectopic pregnancy site; multiple sections may be needed to identify products of conception.

Aneurysms / dissections or other vascular anomalies: Affected and unaffected vessel (site designated).

Pulmonary thromboembolism: Samples of known and suspected thrombi and emboli, including vessel walls, and especially including areas of vascular adherence. Histologic sampling can help differentiate acute thrombosis from chronic, organized thrombosis.

vi. Tissue Sampling at Maternal Autopsy, Other Than for Histologic Evaluation

1. Samples for Microbiologic / Virologic Studies

Microbiologic sampling can be critical to the accurate determination of the cause of a maternal death. The following have been shown to be helpful and could be considered, depending on case circumstances and available resources:

Areas of suspected or identified infection (e.g. uterus, decidua, incision site, skeletal muscle): Obtain sterile sample(s): Divide and send for 1) microbiologic culture, 2) freeze a small section in a sterile container at -20 C, and 3) histologic processing. Frozen tissue can be used for microbiological identification if culture is not available or for more specific molecular microbiological diagnostic studies.

Suspected sepsis: if an antemortem culture was not obtained, use sterile technique to obtain a blood culture (from an upper body vessel / above the diaphragm) or a sterile spleen sample can be cultured and and/or frozen.

Specific concern about puerperal sepsis: additional sampling could include sample of uterus including decidua and any abnormal muscle (necrotizing fasciitis). Organisms of concern include Group A Streptococcus, E. coli, and Clostridium (postpartum uterine infection).

2. Maternal Samples for Possible Genetic Testing :

Blood collected in a lavender-top ethylenediaminetetraacetic acid (EDTA) tube or multiple small (0.1 cm cubes) samples of maternal tissue (skeletal muscle, liver) can be frozen in individual Eppendorf tubes with or without appropriate storage medium (e.g. RNAlater, etc.) for potential genetic testing for pathogenic mutations such as those found in some cardiomyopathies and connective tissue diseases. Skeletal muscle is often better preserved in the postmortem setting and is the tissue of choice. Some authors recommend splenic tissue, but this often shows significant postmortem autolysis [31]. Storage at ultra-low temperatures (-80 C) is optimal if available.

3. Fetal Tissue Preservation for Possible Genetic Testing for Paternity Determination or Other Purposes

Establishment or exclusion of paternity in a pregnancy (for a fetus or other products of conception) can utilize tissue from an embryo or fetus or from fetal components of placental tissue such as umbilical cord or a superficial sample from the fetal surface of the placenta, mainly including fetal membranes and minimal villi. Small pieces (0.1 cm cubes) from each type of tissue can be frozen (-20 C or -80 C) in individual Eppendorf tubes.

4. Samples for Toxicology Testing

In addition to the usual toxicology samples routinely collected at examination (e.g. maternal and/or fetal blood, urine, liver, brain, bile, gastric content), additional samples like

the umbilical cord or meconium can be obtained depending on the circumstances and goals of testing [32, 33]. Umbilical cord testing of a full-term fetus has been shown to reflect prenatal substance exposure in the third trimester [32]. If available, antemortem samples can also be requested from the hospital and a memorandum of understanding with local institutions to retain these specimens longer than usual could be considered.

vii. Antemortem Pathologic Specimens

In some maternal deaths, the placenta may have been delivered at the time of delivery and/or an antemortem or perimortem hysterectomy may have been performed. The pathologic evaluation of these specimens is an important component of the maternal autopsy. The autopsy pathologist may find it helpful to obtain and review reports, photographic images, and histologic slides from any pathology evaluation of these specimens. Additional considerations as follows:

1. Gravid Uterus, Post Hysterectomy:

If a hysterectomy was performed, and the specimen is still available via the delivering institution, the pathologist may request that the surgical specimen be retained after surgical pathology examination and transferred to the ME/C for review by the autopsy pathologist. In general, it is preferred that the hysterectomy or any other relevant surgical specimen be examined via the usual surgical pathology system used by the delivering institution prior to transfer to the autopsy pathologist for review/possible retention. If this cannot be achieved, the autopsy pathologist may perform this examination, using guidelines provided above for the examination of the gravid uterus.

2. Placenta:

Generally in the setting of a potential pregnancy-related or associated death, pathologic examination of the placenta is an important component of the death investigation as it may be key to the identification of the cause of maternal death and/or contributory factors (for example placental abruption, pregnancy-related hypertension, sepsis from amniotic fluid infection / endometritis), maternal or fetal health during pregnancy, and cause of fetal demise.

If the placenta was delivered, the examination may be handled in several ways, depending on the interval between the delivery and death, whether the placenta was already examined by a pathologist associated with the delivery site, and the systems of practice in the jurisdiction.

If the placenta was examined via the usual surgical pathology system used by the delivering institution, and is available after examination, the specimen may be obtained by the ME/C office for review by the autopsy pathologist, along with the corresponding histologic slides and pathology report.

If the placenta was not examined or disposed of, the ME/C may obtain the specimen for evaluation by the autopsy pathologist. An unfixed placenta can be placed in a labelled container and refrigerated for up to 48 hours; for a longer delay before examination, the placenta can be fixed flat with the attached umbilical cord so that it is immersed in a solution of 10% buffered formalin.

Following accepted guidelines for placental pathology examination and interpretation allows for optimal examination and histologic sampling of the placenta. Photographs may be taken of the fetal and maternal surfaces of the placental disc, both fresh and fixed, and of the umbilical cord, as well as of any identified abnormalities. Recommended placental histologic evaluation include sections of the umbilical cord, including near the placental disc attachment, a free membrane roll, a trimmed weight of the placental disc (specifying whether fixed or unfixed), two representative full-thickness central sections of the serially sectioned placental disc, and representative sections of abnormalities [31, 34-36].

viii. Fetal or infant demise in association with a maternal death:

If there has been a fetal or infant demise, autopsy should be considered but is ultimately up to the discretion of the pathologist, with the determination based on the unique circumstances of each case. See Table E for a list of situations which may warrant an internal fetal exam. If a decision is made to NOT perform an internal dissection of the fetus or infant, the pathologist may consider the following procedure: External examination with photographs, standard measurements (such as weight, height, crown-rump length, crown-heel length, heel-toe length, head circumference, chest circumference, abdominal circumference), evaluation for developmental anomalies, and determination of sex (evaluate and photograph the external genitalia and anus). A tissue sample (frozen) may be collected for possible later genetic/paternity/other testing as described above; a good sample is a small piece of skeletal muscle with attached skin from the fetal thigh. Samples may also be obtained for possible toxicology testing [26].

ix. Subspecialty consultation.

Neuropathology and cardiac pathology issues: Consider consultation using usual jurisdictional guidelines and practices.

For issues specific to maternal autopsies, the following specialty consultations could be considered:

-Placental and obstetric (perinatal) pathology.

-Maternal-fetal medicine or obstetric clinical consultation for issues related to clinical records and obstetric diagnostic and therapeutic considerations.

-Specialty laboratory consultation for molecular microbiologic testing or maternal genetic testing.

Common Natural Causes of Pregnancy-Related Death

Epidemiology

The three most common natural causes of maternal deaths in the United States are cardiovascular diseases, hemorrhage, and infection, accounting for nearly 50% of all pregnancy-related deaths [37]. Cardiovascular diseases encompass atherosclerotic coronary artery disease, hypertensive cardiovascular disease, congenital heart disease, valvular disease, vascular aneurysms/malformations, peripartum cardiomyopathy, and other cardiac disease such as conduction defects/hereditary arrhythmias, hypertrophic/arrhythmogenic/dilated cardiomyopathies, myocarditis, and spontaneous coronary artery dissection. Hemorrhagic disorders of pregnancy include ruptured ectopic pregnancy, uterine atony/bleeding, placental abruption, uterine laceration or rupture, placenta previa/accreta and retained products of conception [38-41]. Peripartum genitourinary tract infections and respiratory infections are the most common sources of maternal sepsis and death [42-44]. Other common natural causes of death are venous thromboemboli, hypertensive disorders of pregnancy (preeclampsia and eclampsia), amniotic fluid embolism, collagen/vascular disorders/autoimmune diseases, metabolic/endocrine disorders, pulmonary conditions, and cancer [37-39, 45].

Cardiovascular conditions and hemorrhage are the leading causes of pregnancy-related death across all races and ethnicities and age groups, but the frequency of other natural causes varies among these groups. Asian women have more deaths from thrombotic and amniotic fluid emboli compared to others. Non-Hispanic Black women are more likely to die from thrombotic pulmonary emboli than non-Hispanic White women. Non-Hispanic White women are more likely to die from infections than non-Hispanic Black women

(excluding the 2020 pandemic year) [37-39]. Among peripartum women in the 20-24 and 30-34-year age groups, the most common cause of death is infection. Among peripartum women ages 35-44 years, preeclampsia and eclampsia are the most common causes of death [37].

The most common causes of pregnancy-related deaths also differ by timing in relation to pregnancy. The pregnancy period accounts for approximately 30-37% of pregnancy-related deaths, when hemorrhage from abnormal placental implantation, ectopic pregnancies, and cardiovascular conditions predominate [37, 46]. The first 42 days after pregnancy account for 45-56% of pregnancy-related deaths when infection and hemorrhage are the most common causes [37], but this period also encompasses nearly all deaths from amniotic fluid embolism and hypertension [46]. As many as a third to half of deaths during the first 42 days occur within 24 hours of delivery or termination [40, 46]. An estimated 13-17% of pregnancy-related deaths occur in the 43 days to 1 year following pregnancy during which cardiomyopathy accounts for a third to half of these deaths [37, 46].

The most common causes of pregnancy-related death differ by pregnancy outcome. Most pregnancy-related deaths follow a live birth. All cardiovascular causes and venous thromboemboli are more common after live births, whereas hemorrhage and infectious causes of death are more common after a stillbirth [40, 42, 46]. Infection and hemorrhage are the two most common causes of death following abortion [40].

Older maternal age correlates with an increased relative risk for a pregnancy-related mortality for women of all races, though non-Hispanic Black women are affected disproportionately at every age [40, 47]. More women are becoming pregnant at a later age, and many more of them are entering pregnancy with chronic conditions such as hypertension, cardiovascular diseases, diabetes, chronic kidney disease, obesity, asthma, and sickle cell disease [48].

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is rare and estimated to affect 1 in 2500 to 4000 live births. It is diagnosed clinically when systolic heart failure develops in the last month of pregnancy or within 5 months of delivery, ejection fraction is less than 45%, and no other cause for the heart failure can be found [49]. Risk factors include African-American race, hypertension, older maternal age, and multifetal gestation [49, 50]. The diagnosis of PPCM has clinical and pathologic similarities to dilated cardiomyopathy (DCM) in which both disorders result in left ventricular dilatation without proportionate increase in wall thickness [51]. Unlike the slower progression of DCM, PPCM occurs at a younger age and

tends to have a more rapid clinical course resulting in either recovery or deterioration with heart transplant or death within months after diagnosis [51]. In a small subset of PPCM and idiopathic DCM, genetically similar truncating mutations have been observed, particularly in the gene TTN that encodes the sarcomere protein titin [52]. Other possible etiologies are postulated to include prior viral illness or abnormal immune response with myocardial inflammation [49].

Ruptured ectopic pregnancy

Ruptured ectopic pregnancy is a major cause of maternal mortality in the first trimester [53] and accounts for approximately 2.7% of maternal deaths [46]. The main risk factors for ectopic pregnancy are previous pelvic inflammatory disease, tubal disease, and smoking but also include maternal age >35 years, a history of infertility, and pregnancy while an intrauterine device is in place [54, 55]. The uterus will show decidualization of the endometrium, and diagnosis of ectopic pregnancy can be confirmed histologically by the finding of chorionic villi or fetal parts at the ectopic site or within blood clot from a rupture [53].

Postpartum hemorrhage

The incidence of postpartum hemorrhage varies worldwide from 1-10% [56]. In the US, postpartum hemorrhage increased from 2.7% to 4.3% between 2000 and 2019 [57]. Early postpartum hemorrhage is currently defined by the American College of Obstetricians and Gynecologists as cumulative blood loss of >=1000 mL *or* blood loss accompanied by signs/symptoms of hypovolemia within 24 hours following the birth process (includes intrapartum blood loss) [58]. Signs/symptoms of hypovolemia include a hematocrit drop of >10%, need for a blood transfusion, tachycardia, hypotension, tachypnea, oliguria, pallor, dizziness, or altered mental status [58, 59].

Uterine atony accounts for 70-80% of postpartum hemorrhage [59, 60] and is associated with induced labor, oxytocin use, rapid or prolonged labor, uterine overdistention (multifetal gestation, polyhydramnios, placental abruption, fetal macrosomia), and general anesthesia [59]. Genital tract lacerations and iatrogenic injuries are other common causes of postpartum hemorrhage [59, 60]. Additional causes include the placenta accreta spectrum, retained products of conception, placental abruption, and maternal inherited or acquired coagulation disorders [59, 61].

An infrequent complication of severe postpartum hemorrhage with volume depletion and/or hypotension is pituitary infarction, or Sheehan's syndrome [62, 63]. Most women with hypopituitarism from postpartum hemorrhage will be diagnosed years after delivery with amenorrhea being one of the most common effects [64]. However, life-threatening acute postpartum pituitary infarction may present within days after postpartum hemorrhage with symptoms ranging in severity and including hypotension, shock, seizures, altered mental status, hypoglycemia, hyponatremia, failure to lactate (hypoprolactinemia), central diabetes insipidus, or adrenal insufficiency [62, 63].

Hypertensive Disorders of Pregnancy

Hypertension in pregnancy is defined as a systolic blood pression >=140 mm Hg and/or a diastolic blood pressure of >=90 mm Hg. Gestational hypertension is defined as new onset hypertension after 20 weeks gestation, whereas chronic hypertension is defined as pre-pregnancy hypertension or hypertension diagnosed before 20 weeks gestation [65].

Preeclampsia affects an estimated 5-7% of all pregnancies [66] and presents as hypertension, proteinuria, pulmonary/cerebral edema, liver congestion, and peripheral edema [65, 67]. If severe, it can progress to HELLP (microangiopathic hemolytic anemia, hepatic dysfunction with elevated liver enzymes, low platelets), disseminated intravascular coagulation, and eclampsia with seizures, coma, or death [65, 67]. While the pathophysiology has not been completely elucidated, in some patients it is thought to be related to abnormal placentation in which the maternal immune system fails to properly recognize the fetoplacental unit, causing a release of immune mediators and widespread maternal endothelial impairment, resulting in vasoconstriction, increased capillary permeability, and coagulopathy [67].

Preeclampsia has multiple risk factors including pre-existing chronic hypertension, nulliparity, pre-pregnancy diabetes mellitus, multifetal gestation, high maternal weight, a previous pregnancy with preeclampsia, and genetic predisposition [68-71]. Maternal liver findings can include fibrin deposition in blood vessels and sinusoids, periportal hemorrhage/necrosis, and hepatic rupture [72]. Placental pathology in preeclampsia is marked by features of maternal vascular malperfusion including a small placenta for gestational age, increased syncytial knots, distal villous hypoplasia, infarcts, increased perivillous fibrin, and muscularization of basal plate arterioles [73].

Pregnancy-associated spontaneous coronary artery dissection (PASCAD)

Spontaneous coronary artery dissection is a non-atherosclerotic, non-traumatic cause of myocardial ischemia that can lead to a myocardial infarct and/or sudden cardiac death. Like an acute aortic dissection, the coronary arterial lumen is compressed by the blood within the dissected segment leading to lack of oxygenated blood flow to the associated myocardium. SCAD disproportionately affects women (80-90% of cases) with an average age of 42-52 years [74, 75]. While it is considered a rare entity, it is a common cause of acute coronary syndrome (ACS) in women presenting with myocardial infarct [74].

Pregnancy-associated spontaneous coronary artery dissection is a common cause of acute myocardial infarction in pregnancy and the postpartum period and results in significant morbidity and mortality in this population [76]. The mean age of PASCAD is 33 years of age [77]. Three-fourths of PASCAD present in the postpartum period while approximately 20% present in the 3rd trimester [76-78]. The average time after delivery for presentation of postpartum PASCAD is 23-24 days, but it has been reported as late as 16 months in a postpartum woman who was still breastfeeding [79]. A small percentage of patients have traditional risk factors, including smoking, hypertension, diabetes, and a family history of atherosclerotic coronary artery disease [76, 77]. PASCAD has also been associated with breastfeeding, multiparity, and preeclampsia [74, 77, 79].

More than half of women presenting with spontaneous coronary artery dissection (both pregnancy-associated and unassociated) have a lesion in a single artery, but as many as 40% have dissections involving 2 or more arteries [76, 77]. The left anterior descending coronary artery is most commonly affected while the right coronary artery is least commonly affected [76, 77]. PASCAD, when compared to SCAD not associated with pregnancy, has demonstrated a 2-fold higher risk of multivessel involvement and higher morbidity and mortality [77].

The exact mechanism of SCAD and PASCAD is unknown. It is thought that estrogen receptors may mediate changes during pregnancy that weaken the arterial wall with fragmentation of elastic fibers and loss of mucopolysaccharide components leading to medial weakness [76, 80]. Hormonal and hemodynamic changes of pregnancy may predispose these women to PASCAD [76, 78]. Other arteriopathies have been linked to nonatherosclerotic, spontaneous coronary artery dissection, including fibromuscular dysplasia, connective tissue disorders such as Marfan syndrome and Ehler Danlos syndrome type 4, and systemic inflammatory conditions such as systemic lupus erythematosus and Kawasaki disease [74]. A review of the clinical history with supplemental histology or genetic testing may help identify an underlying etiology.

Venous Thromboembolism

Pregnancy causes temporary changes in the coagulation system that result in relative hypercoagulability, including an increase in clotting factors I, II, VII, VIII, IX and XII, decrease in the natural anticoagulant protein S, and inhibition of fibrinolysis [81]. These coagulation changes are most marked in the third trimester, the end of full-term gestation, and the first few weeks postpartum when the effect may be protective against excessive hemorrhage associated with delivery [81, 82]. The coagulation changes are compounded by decreased blood flow velocity through the deep veins of the lower extremities during late gestation due to the increased size of the uterus putting pressure on the deep venous system [83]. Together these changes confer an increased risk of deep venous thrombosis in pregnant women that ranges from 4 to 6-fold higher than non-pregnant women [84, 85] with significantly elevated risk continuing at least into the first 6 weeks postpartum [82, 84-87]. The risk of deep venous thrombosis with or without pulmonary thromboembolism is highest in women with a pre-existing thrombophilia [86, 88], particularly those with homozygous mutations for Factor V Leiden or antithrombin deficiencies [87, 89]. It is also higher in pregnant women with an age >35 years, cesarean deliveries, postpartum infections, and those with underlying medical conditions such as hypertension, heart disease, sickle cell disease, lupus, obesity, and past thrombosis [86, 88]. VTE is also more common in Black women.

Amniotic fluid embolism

Amniotic fluid embolism (AFE) occurs in an estimated 1 in 13,000 to 50,000 deliveries with a maternal fatality rate of up to 61% in those presenting with classic symptoms [90-92]. The majority of cases occur during labor, but AFE may also occur during cesarean delivery and up to 48 hours after vaginal delivery [91, 92]. AFE has also been reported earlier in pregnancy as a sudden death or associated with abortion [93]. AFE typically presents with one or more symptoms of profound hypotension, dyspnea, hypoxia, altered mental status, acute respiratory distress syndrome, seizures, coma, or cardiorespiratory arrest [91, 93]. Nearly all who initially survive will have clinical or laboratory evidence of DIC [94], and, in some cases, isolated DIC will be the predominant presenting symptom of AFE [95]. Risk factors for AFE are older age, multifetal gestation, male fetus, placenta previa, placental abruption, cesarean delivery, instrumental delivery, uterine rupture, and cervical laceration [91, 96].

AFE is likely the result of a multifactorial, non-IgE immune-mediated, maternal response to amniotic fluid. Studies have shown evidence of complement activation [97], and the

extrinsic pathway of the coagulation cascade is likely activated by tissue factor in the amniotic fluid, initiating a consumptive coagulopathy [91]. The result is transient pulmonary hypertension with right-sided heart failure and hypoxia followed quickly by left-sided heart failure [91, 93]. Maternal tryptase, a marker of mast cell degranulation, may or may not be elevated. While there is evidence that mast cell degranulation occurs in the lungs in AFE, it is not thought to be a major mechanism in the pathology [95].

AFE has no pathognomonic autopsy findings and is a diagnosis based on the clinical signs and symptoms of cardiovascular collapse, respiratory distress, coagulopathy, seizure, or coma with exclusion of other etiologies [90, 91, 95, 96]. The differential diagnoses for AFE primarily include air or thrombotic pulmonary emboli, septic shock, placental abruption, eclampsia, transfusion reaction, acute myocardial infarct, cardiomyopathy, anaphylaxis, aspiration, or uterine rupture. The presence of fetal squamous epithelial cells, mucin from fetal intestine, hair, fat from vernix caseosa, or green-yellow bile pigment from meconium in maternal pulmonary vasculature provide the best laboratory support when AFE is suspected based on clinical symptoms [90]. Polarized light microscopy can help to locate lanugo. Special stains can help identify fetal elements and include cytokeratin stains for fetal squamous epithelial cells, Alcian blue or mucicarmine for mucin, oil red O or osmium stains for fat, anti-meconium antibody stain for ZnCP-1, and anti-mucin antibody stain for TKH-2 [98-101]. However, the presence of fetal elements in maternal circulation is neither reliably sensitive nor specific for AFE and is not required to make the diagnosis [90, 95, 96, 98].

Patients with AFE will also have signs of disseminated intravascular coagulation. At autopsy, there may be generalized bleeding from cut surfaces with widespread petechiae or purpuric ecchymoses. Histologically, microthrombi may be found in small vessels [102].

Violent Death During Pregnancy

Deaths by Suicide or Accidental Drug Intoxication

Deaths by suicide or accidental drug intoxication are leading causes of pregnancy-associated and pregnancy-related death [103], with many occurring in the postpartum period or within 1 year of birth [12]. As the majority of these deaths occur out of hospital, the need for extended support for pregnant individuals with substance use disorders and other maternal mental health disorders beyond the birth hospitalization should be emphasized. Often maternal mental health conditions are present in cases of death by suicide or accidental drug intoxication [104]. In a study of maternal deaths in North

Carolina, 78% of individuals who died by suicide had a known maternal mental health disorder [104]. In a review of suicide or accidental intoxication deaths in Colorado, the decedent was noted to have stopped a medication for a known mental health disorder during pregnancy 48% of the time either on their own or at the recommendation of their obstetric provider despite lack of evidence of harm from the medication [103, 105]. The state-level MMRC form created by the CDC specifically asks the committee to deliberate on whether a maternal mental health condition contributed to the death, which has raised awareness and enhanced focus on this important public health issue.

While drug intoxication deaths are conventionally classified as pregnancy-associated, Smid and colleagues established the Utah criteria to determine if the drug use was pregnancy-related [12] in some cases. These criteria included: pregnancy complications which could have led to drug use, chain of events initiated by pregnancy, or exacerbation of an underlying condition by pregnancy. In 94% of cases of drug-related deaths in Utah, the death was found to be pregnancy-related when applying these criteria. For example, individuals who sought treatment and were in recovery during the pregnancy returned to use postpartum when experiencing stress related to childcare or finances. Similarly, when patients returned to prior use patterns postpartum after a period of recovery, they had had less tolerance than anticipated resulting in unintended overdose.

From a ME/C standpoint, toxicology testing will determine whether drug use contributed to or was responsible for a death and can also help determine whether patients were using prescription drugs, or other drugs that were not prescribed to them. This information is invaluable to MMRCs when deliberating a cause of death, especially for out of hospital deaths with minimal other information or context.

Homicidal Deaths

Although pregnancy-related deaths have fallen sharply in the past century due to the widespread treatment of hemorrhage and infection, medical advances have not reduced mortality during pregnancy due to intentional violence. Fildes, et al. examined records of maternal deaths in Chicago and found that 46.3% were due to trauma, and more than half of the traumatic deaths were homicides [106]. A review of deaths from 1978 to 1991 in New York City found that 63% of women ages 15-44 years who were pregnant or recently pregnant and died traumatically were ruled homicide [107].

The coordinated analysis of multiple sources of information (a technique known as "enhanced surveillance") resulted in marked increases in estimates of maternal mortality from homicide. A 2001 landmark study by Diane Cheng, MD, and Isabelle Horon, DrPH of

the Maryland Department of Health and Mental Hygiene also took a multipronged approach to the issue of identifying and classifying causes of death of pregnant or recently-pregnant women [108]. By simultaneously examining death certificates, linking birth and fetal death records, and reviewing medical examiner files, Cheng and Horon found that a pregnant or recently-pregnant woman residing in Maryland from 1993 to 1998 was more likely to be murdered than to die in any other manner; at least 20 percent of women in their study who died during pregnancy were victims of homicide [108]. Surveillance performed on a national level also found homicide to be among the leading manners of death for pregnant women [109] and a published response noted that, due to limitations on the availability of records, the study likely represented a significant underestimate of the frequency with which pregnant women are murdered [110]. In response to the information generated regarding the frequency with which pregnant women are murdered, the US Standard Certificate of Death was revised to gather more information on the pregnancy status of decedents. In the 2003 revision, the NCHS added a request for information regarding the decedent's pregnancy or recent post-partum status at the time of her death [111].

Despite death certificate redesign and increased awareness of the issue, the frequency of pregnancy-related homicide is still likely underestimated. Horon and Cheng evaluated the efficacy of death certificates checkboxes from the years 2001 to 2008 with regard to identifying current or recent pregnancies, and found that while the checkbox format was very effective at identifying deaths from natural causes, more than 50% of deaths due to homicide, accidents, suicides, and substance abuse failed to identify a current or recent pregnancy on the death certificate [112].

Pregnancy terminations

Abortions, both spontaneous and induced, should be included when considering whether a decedent had a pregnancy within one year of the time of death. Even with an early pregnancy, normal physiology is altered, which places individuals at increased risk of many medical complications. In addition, knowledge of a pregnancy can sometimes prompt changes to medical care that then contribute to the cause of death (e.g. withholding therapies in the setting of a known pregnancy).

Medically, an abortion is defined as the termination of a pregnancy, whether spontaneous or induced [113]. Spontaneous abortions are defined as resulting from a natural process or underlying condition and are colloquially often referred to by the term miscarriage. The complications of a spontaneous abortion have significant overlap with the complications

of live births, as previously discussed in this document, including cardiovascular disease, hemorrhage, and infection. In addition to the usual complications of pregnancy there is potential for additional complications related to an incomplete abortion or retained products of conception [114].

Induced abortions can be divided into medical and surgical abortions. The complications and deaths associated with an induced abortion vary depending on the method that is used, and as with spontaneous abortion, there is overlap with complications of pregnancy in general as described above. There are not current data delineating differences between the autopsy findings of legal versus illegal abortions.

Methods of medical abortion include progesterone inhibition/antagonism, induction of myometrial contractions, and inhibition of trophoblast development. These methods are not recommended after 9 weeks gestation and in general they may require more clinic visits than a surgical abortion to ensure abortion completion [115]. Methods of surgical abortion include manual vacuum aspiration, dilation and curettage, or dilatation and evacuation (which is generally performed in the second trimester).

Complications of medical abortion include hemorrhage, nausea or vomiting, pain, retained products of conception, and an overall lower rate of success when compared with surgical methods [115]. Rare complications of surgical abortion include uterine perforation, hemorrhage, and infection [116-119]. The risk of complications increases with increasing gestational age and increasing size of the fetus [114].

Surgical abortion can be life-saving in the setting of an incomplete spontaneous abortion resulting in maternal hemorrhage, or in the setting of a septic abortion in which the products of conception must be removed to adequately treat the infection. However, if a surgical abortion is carried out by persons lacking the necessary skills or in an environment lacking minimal medical standards or both, the potential for complications increase [120].

Guidelines for Death Certification

Accurately completed death certificates are the main source of data used to assess maternal mortality in the United States and are an important component of the public health evaluation of maternal deaths. Accurate certification of deaths associated with pregnancy requires two main actions:

- Determination of the cause and manner of death.
- Identification of the decedent's pregnancy status within the previous year.

While general guidelines for the completion of death certificates are available from the US National Center for Health Statistics (NCHS) [121, 122], including resources on medical death certification for physicians and other medical certifiers [123] and for medical examiners and coroners [124], these references do not provide guidelines for the documentation of deaths associated with pregnancy. To address this need, a NCHS-convened multi-disciplinary group developed and published a reference guide focused on the certification of deaths associated with pregnancy [3]. In addition to providing definitions and clear instructions for the completion of these death certificates, the guide also provides sample cases with certifications that illustrate and clarify the use of the guidelines in various types of pregnancy-associated deaths. These guidelines are recommended for use by all providers documenting deaths associated with pregnancy.

Factors critical to the accurate certification of deaths associated with pregnancy include the following [3].

DETERMINATION OF CAUSE AND MANNER OF DEATH: If pregnancy caused or contributed to death, whether during the pregnancy or within the previous year, it is important that words related to pregnancy appear in either the Cause of Death Section or the Other Significant/Contributory Conditions Section (Parts I and II of the US Standard Certificate of Death, respectively).

PREGNANCY STATUS WITHIN THE PREVIOUS YEAR: The pregnancy checkbox is be used to document the pregnancy status of all female decedents of reproductive age (approximately 10-50 years) using information obtained by medicolegal death investigators or medical death certifiers. Data from the checkbox supports vital statistics coding to correctly classify a pregnancy-associated death. Completion of the pregnancy checkbox requires indicating one of the following, using available sources such as family interviews, medical records and tests, and postmortem evaluations:

- Not pregnant within the past year
- Pregnant at the time of death
- Not pregnant, but pregnant within 42 days of death
- Not pregnant, but pregnant 43 days to 1 year before death
- Unknown if pregnant within the past year

In some jurisdictions additional information related to pregnancy status is captured on the death certificate, such as outcome of pregnancy (e.g. live birth, ectopic pregnancy, fetal death, miscarriage) and date of that outcome [125].

The addition of the Pregnancy Checkbox to the US Standard Certificate of Death occurred in 2003 to facilitate the accurate identification of deaths associated with pregnancy [126].

If pregnancy status is not accurately documented in this section, maternal deaths will be incorrectly reported, which will result in inaccurate maternal mortality statistics [3].

Adoption and promotion of these guidelines by ME/C offices and their professional organizations will contribute to more accurate and consistent death certification for deaths associated with pregnancy and more accurate maternal mortality data.

Forensic Pathology Involvement in Maternal Mortality Review Committees (MMRCs)

MMRCs have as their goal the elimination of preventable pregnancy-related deaths in the United States. These state and jurisdiction level multi-disciplinary committees are supported by the CDC, including facilitation of standardized MMRC data collection through the use of the CDC's Maternal Mortality Review Information Application (MMRIA). A recent position statement from the Society for Maternal-Fetal Medicine "strongly supports state maternal mortality review committees as a mechanism for comprehensive identification, review, and analysis of deaths during and within one year of pregnancy", and recommends that "each state have an active maternal mortality review committee" that at least meets the minimum standards described in the position statement [127],

MMRC Mission: The MMRC monitors maternal mortality through in-depth case reviews, categorizes maternal deaths based on cause of death and pregnancy relatedness, assesses contributing factors and preventability, and recommends intervention strategies at various levels across the healthcare landscape, thereby prioritizing interventions with the greatest opportunity for impact. The MMRC identifies the annual number of maternal deaths, derives a pregnancy-related mortality ratio, and identifies trends and risk factors to develop actionable strategies to eliminate preventable maternal deaths.

ME/C understanding of the composition, expectations, and outcomes of an MMRC is vital given their involvement in the investigation of pregnancy-associated and pregnancy-related deaths. Additionally, the CDC recommends a forensic pathologist be a member of the multidisciplinary MMRC. ME/C contributions to maternal death investigations and MMRCs will support more comprehensive data from which progress towards those goals can be monitored.

Querying Maternal Deaths: The MMRC uses various methods for the identification of maternal deaths of residents of the jurisdiction [128]. These include many of the same methods that have historically been available to researchers. The NVSS / NCHS / CDC database uses literal causes of death from death certificates to assign ICD 10 codes to causes of deaths during pregnancy up through 42 days after the end of a pregnancy. This categorization aligns with the WHO definition of a maternal death.

The CDC Pregnancy Mortality Surveillance System (PMSS) utilizes clinically trained medical epidemiologists to determine pregnancy-related, pregnancy-associated, and non-pregnancy-related deaths by reviewing death certificates linked to fetal death or and birth certificates, both during the pregnancy and up to 365 days postpartum. If the death is determined to be pregnancy-related, it is included in the database and assigned a PMSS-identified cause of death. This database provides pregnancy-related mortality ratios. These death records are voluntarily submitted from 54 reporting areas to CDC for this purpose. Causes of death are coded based on ACOG and CDC Maternal Mortality Study Group system established in 1986 [39, 123]. This data is collated and published on the CDC website.

State and local MMRCs can perform local queries of death records, pregnancy status checkboxes, linked birth /fetal / death records, medical records, social services records, and autopsy information to capture even more maternal deaths. Some MMRCs have additional protocols for identifying maternal deaths, such as direct hospital reporting, media reports, or obituary searches.

The ME/C on the MMRC: The ME/C on the MMRC can make significant contributions to the committee and to the cases reviewed. Most members of the MMRC have had limited experience working with a ME/C as they are typically caring for young, healthy persons. The ME/C's investigations and autopsies are an important source of mortality information and associated social determinants within a community. The ME/C is well-positioned to identify early changes in mortality trends or emerging health crises, such as an infectious disease outbreak or spike in drug overdoses. The ME/C educates the MMRC on how clinical and autopsy findings relate to a proximate cause of death. Without ME/C expertise the quality of the interpretation of autopsy and other postmortem information on causality may be compromised. Additionally, the collegial work builds rapport with other stakeholders who can advocate for support of the death investigation system within the jurisdiction.

Components of the review: Reviews of each identified case are performed. A summary of the components of the review is listed in Table F.

MMRC Actions and Outcomes: The MMRC reports its data and recommendations on a regular and annual basis to the state and CDC [128] . The data is published at the state and federal levels and interventions are discussed [129]. MMRCs offer education to the members on topics such as social determinants of health [130], implicit bias, racism, and intimate partner violence. MMRCs promote maternal health campaigns and write and support legislation aimed at improving all aspects of maternal care [131].

Although all 50 states have had MMRCs at some point, changes in legislation around abortion have led several MMRCs to become defunct, not renew their charters, or even become the subject of media attention. It is imperative that the ME/C remain independent and objective in their role on these committees and use practical and scientific evidence based decision making [132].

Summary of NAME Position on Public Health and MMRCs: ME/Cs play an extremely important role in the public health of maternal mortality. MMRCs should be supported and a permanent feature within state and local public health. The ME/C is a vital member the MMRC. The ME/C can use information learned in the MMRC experience to sculpt their death investigation system to offer thorough investigations of maternal deaths. Improvements in maternal care occur through this multidisciplinary approach, and ultimately maternal mortality will decline through these efforts.

Future Directions/Research

In order to reduce maternal mortality rates in the US and abroad, targeted research is needed in areas where evidence is currently insufficient or inconclusive. For the purposes of this paper, such research can be broadly categorized as pertaining to forensic pathology *or* public health, although these fields are not distinct but intimately intertwined.

From a pathology perspective, additional studies on the pathophysiology of poorly understood syndromes such as amniotic fluid embolism, peripartum cardiomyopathy, and acute fatty liver of pregnancy are needed to clarify the mechanisms underpinning their morbidity and mortality and inform how these conditions can be accurately diagnosed

postmortem. Additional studies to further validate methods of detection of early pregnancy in a variety of postmortem fluids are encouraged. Forensic, gynecological, and perinatal pathologists alike would benefit from further gross and histopathologic references for the postmortem evaluation of pregnancy. To maximize usefulness, such resources should highlight normal findings as well as disease states and be inclusive of the early pregnancy period and those findings associated with pregnancy termination.

The field of forensic pathology in general would be enriched by the validation of additional postmortem biomarkers as diagnostic aids. Likewise, large-scale genomic studies of deaths unexplained after complete autopsy would have significant relevance to maternal health. Molecular biology has great potential to provide a better understanding of genetic predispositions towards peripartum cardiomyopathy, arrhythmias, or thromboembolism. Research is also needed on the use of postmortem computed tomography (CT) and magnetic resonance imaging (MRI) to supplement or guide autopsy in maternal deaths. Such non-invasive methods can support or replace traditional autopsy in culturally sensitive cases. Studies on the effectiveness of postmortem MRI/CT in diagnosing hemorrhage, embolism, or organ rupture may be particularly promising.

From a public health standpoint, additional research on the accuracy and quality of maternal mortality statistics in needed [128, 133], with a possible role for artificial intelligence (AI) or other digital innovations. The ME/C, in particular, can help broaden the understanding of maternal mortality beyond hospital records. By collaborating with public health and obstetrics to integrate forensic data into national maternal mortality statistics, additional late and pregnancy-associated maternal deaths may be identified and more thoroughly investigated [110, 134]. Comprehensive attempts to correlate postmortem findings with clinical and social histories may further clarify the mechanisms by which factors such as race, socioeconomic status, healthcare access, or systemic bias contribute to maternal mortality, and thereby assist in formulating preventative strategies. The ME/C can further delineate the scope of this issue with the application of routine postmortem testing for early pregnancy [135].

There is a dearth of information regarding maternal mortality rates with respect to type of obstetric care provider and birth setting. Existing studies focus largely on neonatal outcomes or expanding the use of non-physician providers in low resource areas. Research is also lacking regarding the magnitude and type of impact climate change has had on global mortality rates in general.

Strong health systems are critical for reducing maternal mortality rates. However, many women, especially in poor or rural areas, die due to delays in receiving adequate care

[136]. The reasons for this are multifactorial and include issues such as transportation, education, and the availability of facilities and appropriately trained staff. A study of 24 European Union countries (1981–2010) previously found that a 1% annual decrease in government healthcare spending was associated with a 10.6% rise in maternal mortality [137]. In the US, Medicaid expansion under the Affordable Care Act has been linked to 7 fewer maternal deaths per 100,000 live births [138]. Research is needed to assess the ways in which ongoing US healthcare policy reforms influence maternal outcomes.

Reducing maternal mortality requires comprehensive and multidisciplinary research that looks beyond clinical interventions. Strengthening the evidence base will support policies aimed at promoting health equity and improving maternal health outcomes worldwide, and the ME/C has a significant role.

Conclusion

The ME/C has a vital role to play in the investigation of pregnancy-related and pregnancy-associated deaths. It is essential that these deaths are reported to the ME/C so that a thorough and complete investigation can be performed, allowing public health stakeholders to have the opportunity to gather accurate data. A complete and accurate account of how women are dying affords the opportunity to prevent future deaths. A thorough investigation be performed to determine the cause and manner of death and to facilitate collaboration between the ME/C and local and regional departments of health to share this important information.

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Tables

Table A: Definitions

Maternal death (WHO): the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes [139]

Late maternal death (WHO): the death of a woman from direct or indirect obstetric causes, more than 42 days but less than one year after termination of pregnancy [139]

Pregnancy-related (WHO): the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death [140]

Pregnancy-related (CDC): the death of a woman while pregnant or within 1 year of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes [23]

Pregnancy-associated (CDC): death that is physiologically unrelated to the pregnancy and occurs within 1 year of the pregnancy's end [23]

Table B: Screening questions for the medicolegal death investigator to consider

Has the decedent ever been pregnant?

How many times has the decedent been pregnant?

How many live births has the decedent experienced?

If any live births, what was the method of delivery?

Any history of pregnancy complications (pregnancy-associated diabetes, hypertension, thromboembolism, difficult delivery in the past)?

If pregnant at the time of death, what is the estimated gestational age?

If pregnant at the time of death, any recent symptoms related to the pregnancy (e.g. fetal movement, discharge, leakage, bleeding, pain)?

Table C: Histologic sections to be considered

Heart and coronary arteries (2 full thickness sections of ventricles)

Lungs (1-2 sections from each lobe)

Kidney

Liver

Spleen

Adrenal glands

Brain with leptomeninges

Pituitary (complete)

Cervix (including ecto and endocervix)

Bilateral ovaries

Fallopian tube (if abnormal)

Non-gravid uterus (several full thickness sections of endomyometrium)

Table D: Histologic sections of the gravid uterus to consider

Uterus without placenta, full thickness, location specified

Uterus with attached placenta, full thickness, location specified

Central and peripheral placental disc

2 samples of the umbilical cord (including one near the placental disc attachment)

Free membrane roll

Placental abnormalities

Uterine abnormalities

Bilateral parametrial vessels

Table E: Situations when internal fetal examination may be considered

Homicidal violence as the cause of death

Suspicious circumstances

External evidence of unexpected fetal trauma

External evidence of unexpected congenital abnormality

Unknown cause of maternal death

Table F: Components of MMRC Review

Completeness of case materials

Quality of autopsy / death investigation

Cause and manner of death

Circumstances surrounding death

Pregnancy relatedness

Preventability

Contributory factors

Recommendations for action