Maternal Death and Its Investigation

Jack Garland, Dianne Little

ABSTRACT

Maternal deaths are a leading cause of death in young females worldwide, particularly in developing countries. Maternal mortality ratio, the number of maternal deaths per 100 000 live births, averages 240 in developing regions, but only 16 in developed regions.

Causes of maternal and pregnancy-related deaths can be subdivided into three broad categories. Direct maternal deaths result from obstetric complications of the pregnant state (i.e., pregnancy, labor, and puerperium) from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above. Indirect maternal deaths result from previously existing diseases or diseases that developed during pregnancy, and which are not due to a direct obstetric cause, but are aggravated by the physiologic effects of pregnancy. Incidental maternal deaths are those from causes unrelated to pregnancy or the puerperium, including accidental deaths and homicide.

Maternal deaths carry significant short- and long-term impacts for family members and the role of the pathologist is an important part of the wider knowledge-gathering process that can contribute to changes in maternal mortality rates. This paper reviews the clinical and pathological features of common pregnancy-related disorders and gives guidelines for performing an autopsy related to maternal death. *Acad Forensic Pathol.* 2018 8(4): 894-911

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ETHICAL APPROVAL

As per Journal Policies, ethical approval was not required for this manuscript

STATEMENT OF HUMAN AND ANIMAL RIGHTS

This article does not contain any studies conducted with animals or on living human subjects

STATEMENT OF INFORMED CONSENT

No identifiable personal data were presented in this manuscript

DISCLOSURES & DECLARATION OF CONFLICTS OF INTEREST

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest

FINANCIAL DISCLOSURE

The authors have indicated that they do not have financial relationships to disclose that are relevant to this manuscript

KEYWORDS

Forensic pathology, Maternal death, Autopsy

INFORMATION

ACADEMIC FORENSIC PATHOLOGY: THE OFFICIAL PUBLICATION OF THE NATIONAL ASSOCIATION OF MEDICAL EXAMINERS

©2018 Academic Forensic Pathology International • (ISSN: 1925-3621) • <https://doi.org/10.1177/1925362118821485>

Submitted for consideration on 28 Oct 2018. Accepted for publication on 16 Nov 2018

INTRODUCTION

The World Health Organization (WHO) defines maternal death as:

...the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (1).

Pregnancy-related death is similarly defined by the WHO as “*the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death*” (1). Given their closely-related definitions, many papers and investigative bodies use the term maternal death when referring to the WHO definition of pregnancy-related deaths.

Worldwide, maternal mortality is unevenly distributed with the vast majority of maternal deaths taking place in developing countries, particularly across Southern Asia and Sub-Saharan Africa where 30% and 57% of global maternal deaths in 2008 occurred, respectively (2-4). Maternal deaths are a leading cause of death in young females (10-24 years of age) worldwide at 15%, with most of these deaths occurring in developing countries (5). A common international measure of maternal mortality rates is via maternal mortality ratio (MMR), which is defined as the number of maternal deaths per 100 000 live births (2, 6). Due to issues such as local registration of death reporting quality, chosen datasets, and differences in statistical analysis, MMRs are at risk of underestimation and can vary between studies (2, 7). In a 2012 joint review involving the WHO and the United Nations International Children's Emergency Fund (UNICEF), 40 countries had a high MMR (≥ 300 maternal deaths per 100 000 live births), the highest of which were Chad and Somalia, with respective MMRs at 1100 and 1000 (3). Contrasting with developing regions where the average MMR was 240, the average MMR in developed regions was 16, although a range of MMRs was noted between developed countries, such as Italy ($n = 4$), Australia ($n = 7$), the United Kingdom ($n = 12$), and the United States of America ($n = 21$) (3).

The Millennium Development Goals established by the United Nations in 2000 aimed to reduce maternal mortality by 75% between 1990 and 2015 as part of a general global trend of reduction in maternal mortality (8). Contrary to the global overall reduction in maternal mortality of 44% over this time period (8), maternal mortality in the United States of America (USA) is amongst the highest in the developed world and has actually increased over this same period (2, 3, 9). Whilst MMRs in most other developed countries have decreased or remained stable over this period (2, 3), the Centers for Disease Control and Prevention (CDC) estimate an increase in USA MMR between 1987 and 2014 from 7.2 to 18.0 (9). A systematic analysis for the Global Burden of Disease Study had higher estimates of an increase in USA MMR from 16.9 to 26.4 from 1990 to 2015 (2).

The precise causes for the apparent increase in USA maternal mortality over this period are not clear, although increased identification through computerized data gathering and reporting are thought to have contributed to these figures (9, 10). Increases in comorbidities that affect the risk of pregnancy complications such as hypertension, diabetes, and heart disease are also suspected to have contributed to an increase in USA MMR, whilst a 15-month spike in MMR between 2009 and 2010 was attributed to the H1N1 influenza A pandemic at that time (9). Maternal deaths in the USA are also not evenly distributed, with black women having a MMR that is approximately four times greater than that of white women (9-12). Over the period of 2011 to 2013, the MMR of non-Hispanic black women was estimated as 43.5 compared to 12.7 for non-Hispanic white women (10). Socioeconomic factors such as education and access to healthcare in addition to medical comorbidities are considered to contribute to much of this difference (12).

Causes of maternal and pregnancy-related deaths can be subdivided into three broad categories: direct maternal deaths, indirect maternal deaths, and incidental maternal deaths (1, 6, 13) (**Table 1**).

Worldwide, direct causes account for 86% of maternal deaths, with the most common causes being

hemorrhage and hypertensive disorders, whilst death from maternal hemorrhage is overwhelmingly more common in developing compared to developed countries (2). Factors such as access to safe health care, antibiotics, and maternal monitoring, where available, contribute to lower rates of maternal complications leading to death (6, 8). In the USA, the most common causes of maternal death are indirect, with the most frequent being cardiovascular diseases (15.2%), noncardiovascular medical diseases (14.7%), infection (12.8%), hemorrhage (11.5%), cardiomyopathy (10.3%), pulmonary embolism (9.1%), cerebrovascular accident (7.4%), hypertensive disorders of pregnancy (6.8%), and amniotic fluid embolism (5.5%) (9). The most common causes of maternal death in the USA differ depending on pregnancy outcome, where in cases of stillbirth or ectopic pregnancy, hemorrhage is the most common cause of death and makes up 21.4% and 94.4% of maternal deaths respectively (7).

Race and sociodemographic factors also influence the common causes of maternal death, with hemorrhage being the most common cause of death in the USA for foreign-born white, black, and Hispanic women and USA-born Hispanic women compared to the higher rates of cardiovascular death amongst white and black USA-born women (12). Despite increasing rates of USA maternal mortality and the influence of sociodemographic factors on maternal death, the low percentage of maternal deaths compared to mortality in the wider population means that maternal autopsies are a rare encounter for any individual pathologist.

Maternal deaths carry particularly significant short- and long-term impacts for family members and the role of the pathologist is an important part of the wider knowledge-gathering process that can contribute to

changes in maternal mortality rates. The purpose of this paper is to review the clinical and pathological features of common pregnancy-related disorders and to give guidelines for performing an autopsy related to maternal death.

DISCUSSION

Direct Maternal Deaths

Pregnancy-Induced Hypertensive Disease (Preeclampsia, Eclampsia, and HELLP Syndrome)

The diagnostic criteria for preeclampsia were changed in 2014 by the International Society for the Study of Hypertension in Pregnancy (ISSHP) to:

...de novo hypertension developing after 20 weeks of gestation combined with proteinuria (>300mg per day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological or hematological complications, uteroplacental dysfunction or fetal growth restriction (14, 15).

Eclampsia is progression of the disorder with development of cerebral symptoms such as visual disturbance, headache, dizziness, seizure, decreased level of consciousness, or coma. It occurs in approximately 0.5% of pregnancies (16). Intracerebral hemorrhage is the most common cause of death, particularly in older women, accounting for approximately 60% of fatalities (17).

Preeclampsia occurs in approximately 3-8% of pregnancies globally (18-20). There is a higher rate in developing countries (15) where it is responsible for

Table 1: Causes of Maternal Death

Type of Death	Definition
Direct Maternal Deaths	Those resulting from obstetric complications of the pregnant state (i.e., pregnancy, labor and puerperium) from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.
Indirect Maternal Deaths	Those resulting from previous existing diseases or diseases that developed during pregnancy, and which were not due to a direct obstetric cause, but were aggravated by the physiologic effects of pregnancy.
Incidental Maternal Deaths	Deaths from unrelated causes that happen to occur in pregnancy or the puerperium.

up to 20% of maternal fatalities (21). In the USA in 2010, 3.8% pregnancies were affected by preeclampsia (18) and the rate is not decreasing with time (14, 16). Risk factors for preeclampsia include primiparity, age greater than 40 years, obesity, diabetes mellitus, multi-fetal pregnancy, and positive family history (14, 19).

The pathophysiology of preeclampsia is not completely understood. However, it is thought that abnormal placental vascular remodelling may result in placental ischemia with release of inflammatory factors to the maternal blood, causing vascular endothelial dysfunction with generalized vasoconstriction and subsequent

multiorgan dysfunction (15, 18). There are no reliable clinical screening tests to predict risk of preeclampsia (14).

Pathology of Preeclampsia

Histology of the uterus in preeclampsia shows fibrinoid necrosis in the vessel walls with numerous lipophages cuffed by mononuclear inflammatory cells (**Image 1**). This change is seen especially in the spiral arteries of the decidua parietalis, the basal arteries of the decidua basalis and myometrium, and in the myometrial segments of the spiral arteries in the placental bed (22). In addition, there is failure of the normal

Image 1: Fibrinoid necrosis with lipophage cuffing in placental bed vessel walls in a case of preeclampsia (H&E, x100). Image courtesy of Dr. TY Khong, Adelaide, Australia.

physiological adaptive changes in the spiral arteries of the placental bed to extend beyond the deciduo-myometrial junction (22). In contrast, in uncomplicated essential hypertension, although there is hyperplastic arteriosclerosis especially in the myometrial segments of the spiral arteries, vascular changes are otherwise normal, including the depth of endovascular trophoblastic invasion.

Other pathological changes which may be seen include glomerular capillary endotheliosis (swelling of endothelial cells with occlusion of capillary lumens) in the kidneys, “flame” hemorrhages in the left ventricular outflow tract of the heart, and adrenal hemorrhage and necrosis (20).

HELLP Syndrome

HELLP stands for hemolysis, elevated liver enzymes, low platelets, which is descriptive of the features of this disorder, first described in 1982. Two-thirds of cases occur in the third trimester and one third are postpartum (23).

HELLP occurs in approximately 5-12% of patients with severe preeclampsia (17, 21). At risk groups are very old or young maternal age, multi-fetus gestation, multiparity, and a past history of preeclampsia or HELLP. The pathogenesis is thought to be damage to vascular endothelial cells by activated platelets and inflammatory factors which activate the coagulation cascade with development of thrombotic microangiopathy (23, 24).

One percent of patients develop severe disease with complications including disseminated intravascular coagulation (21%), placental abruption (16%), acute kidney disease (8%), and spontaneous rupture of the liver. It is thought that spontaneous rupture of the liver may be a result of inflammation with blood flow obstruction which causes liver swelling and hepatocellular necrosis (particularly peri-portal) with intrahepatic hemorrhage and development of a subcapsular hematoma that may rupture spontaneously to cause hemoperitoneum (17, 21, 23).

In preeclampsia, eclampsia, and HELLP syndrome, particular efforts must be made to obtain relevant clinical history, examination notes, and antemortem investigation results, due to the high importance of clinical information in assisting the diagnosis of these conditions.

Peripartum Hemorrhage

Peripartum hemorrhage is commonly due to placental abnormalities, but may also be caused by genital tract tears, either spontaneously-occurring during parturition or iatrogenic. Placental abnormalities include placenta previa, abnormally adherent placenta (e.g., accreta, increta, percreta), placental abruption, and retained placenta. These may be related to a previous cesarean section scar.

Placenta previa is the implantation of the placenta in the uterine lining near or over the cervical opening and is usually diagnosed clinically. Its demonstration at autopsy in the undelivered patient requires removal of the uterus *en bloc* with the cervix and upper vagina to show the placenta covering the lower segment of the uterus and/or across the internal os. Abnormally adherent placenta (**Image 2**) occurs in one in 540 to one in 93 000 pregnancies (22). It is often associated with placenta previa and/or previous uterine surgery. Examination shows direct apposition between villous and trophoblastic elements and the myometrium without an intervening layer of decidua. Placenta percreta is the most severe form and villi can penetrate through the uterine or cervical wall to adjacent structures, such as the bladder.

Placental abruption is the early detachment of the placenta from the uterus wall prior to delivery. This may be traumatic or nontraumatic in etiology. In traumatic placental abruption, for example caused by blunt force trauma to the abdomen secondary to a fall, motor vehicle collision, or homicide, there may be little or no external evidence of injury despite the internal trauma. It is important to look for patterned imprint injuries to the abdomen in these cases. Nontraumatic placental abruption may be associated with maternal hypertension, cigarette smoking, or use of stimulant

Image 2: Placenta accreta – the placenta is firmly attached to the uterine wall. Courtesy of Dr T. Y. Khong, Adelaide, Australia.

drugs (such as cocaine and amphetamines). In the latter case, the placenta may appear normal on microscopy.

Pulmonary Embolism and Venous Thrombosis

Venous thrombosis has a five times increased risk in pregnancy due to the hypercoagulable state in pregnancy, vascular trauma (during normal vaginal birth and/or with medical intervention procedures), and venous stasis (particularly if there is immobility due to bed rest). Hypercoagulability persists until about two months postpartum. It is a normal pregnancy change that protects against excessive hemorrhage during delivery. There is an increase in clotting factors and fibrinogen along with decrease in components of the fibrinolytic system (17, 20). The risks are increased if there is an underlying mutation in prothrombin or Factor V Leiden and in cesarean section compared to vaginal birth. There is also an increased risk of cerebral venous sinus thrombosis, particularly of the superior sagittal sinus.

Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) presents as sudden onset shortness of breath and circulatory collapse in a previously asymptomatic woman during or shortly after delivery. Amniotic fluid embolism occurs in approximately one in 25 000 deliveries (22). The death rate is 60-85% and accounts for approximately 5-10% of all maternal deaths (20, 25).

Amniotic fluid embolism is caused by a tear in the placental membranes and uterine body, cervix, or vagina which allows amniotic fluid to enter the maternal venous system. The tear may be difficult to demonstrate at autopsy. The amniotic fluid can cause physical obstruction of the pulmonary microvasculature and vasospasm with resultant right heart failure and hypoxia (17, 22, 25). There may also be activation of complement system and/or anaphylactoid reaction to the amniotic fluid (25, 26). If there is a period of survival, there is development of dissemination intravascular coagulation (DIC) and acute renal failure develops.

Risk factors include uterine hypercontractility, instrumental procedures (e.g., cesarean section, use of forceps, vacuum extraction), high maternal age, placental abruption, uterine rupture, maternal diabetes mellitus, and fetal macrosomia. Amniotic fluid embolism requires a pathological diagnosis. There are no clinical diagnostic tests for the condition. Amniotic fluid emboli are rarely seen macroscopically and may include lanugo hairs, vernix caseosa, and/or meconium.

The maternal lung should be examined histologically for components of amniotic fluid in the pulmonary arterial system such as epithelial squames from fetal skin (which must be differentiated from sloughed maternal endothelial cells, the latter having nuclei, unlike the squames), lanugo hairs (which may be seen under polarised light [20]), vernix caseosa (fatty), mucin from the fetal intestine and bile from meconium (**Image 3**). Sections should be taken from all lobes of both lungs. Stains have been developed to show all of these amniotic fluid components, such as the modified Attwood stain (alcian green/blue-phloxine-tartrazine). Immunohistochemical stains may also be performed on the maternal lung looking for components of amniotic fluid. These include cytokeratin to show epithelial squames (17) and zinc coproporphyrin 1 (ZnCP-1) for meconium (25). Zinc coproporphyrin 1 and sialyl-Tn, components of meconium, may also be assayed in the maternal blood (25).

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is defined as:

...the development of cardiac failure between the last month of pregnancy and five months postpartum, the absence of an identifiable cause, the absence of recognisable heart disease prior to the last month of pregnancy, and left ventricular systolic dysfunction demonstrated by echocardiographic criteria (27).

Peripartum cardiomyopathy occurs in one in 2289-4000 live births in the USA (27-29) and it carries high mortality and morbidity rates (up to 50% mortality) (17).

The cause of peripartum cardiomyopathy is unknown, but is probably multifactorial, including myocarditis, micro-chimerism, increased apoptosis with inflammation, and maladaptive response to pregnancy-induced hemodynamic changes. There may be a genetic basis, but no specific genetic defects have been yet identified (27-29).

The risk of peripartum cardiomyopathy is increased in multiparity, high maternal age, multi-fetal pregnancy, preeclampsia, black women, and women with high prolactin levels (27-29).

Peripartum cardiomyopathy is a type of dilated cardiomyopathy, and this reflected in the morphology of the condition. Pulmonary congestion and edema may

be present, and cardiomegaly with left ventricular hypertrophy in particular may also be demonstrated (29). Pathological examination of the heart shows four chamber dilatation with myocyte hypertrophy, interstitial fibrosis, and scattered inflammatory cells on microscopy (17, 27).

Complications of Early Pregnancy

Complications of early pregnancy include ruptured ectopic pregnancy (**Image 4**) and problems related to termination of pregnancy.

Approximately 2% of pregnancies occur in an ectopic site – other than in the normal intrauterine location (30). The most common site (90%) (30) is the fallopi-

Image 3: Maternal lung arteriole in amniotic fluid embolism showing epithelial squames in the lumen (H&E, x400). Courtesy of Dr T. Y. Khong, Adelaide, Australia.

an tube, but ectopic pregnancies can also occur in the ovary and peritoneal cavity. Autopsy requires careful examination of the uterus, adnexa, and peritoneal cavity in women of childbearing age in order to identify ectopic pregnancies.

Macroscopically, the fallopian tube is enlarged and filled with blood. If rupture has occurred, there may be massive hemorrhage into the peritoneal cavity.

Microscopy shows an embryonal sac and chorionic villi with invasion of the wall of the fallopian tube by trophoblast. Collection of DNA specimens from the gestational material, or, at minimum, preservation

of the ectopic tissue in a block, should be performed should potential paternity questions arise.

Deaths related to termination of pregnancy are more common in countries with restrictive policies regarding legal termination of pregnancy where infection and/or hemorrhage are the most common causes of death. Risk factors include younger women and gestation over 14 weeks (3).

In the USA, for therapeutic terminations of pregnancy the death rate is approximately 0.7/100 000 procedures. The risk increases with increasing gestational age and is three times greater for black women (30).

Image 4: Ectopic pregnancy (H&E, x50). Image courtesy of Dr. C Milroy, Ottawa, Canada.

Most deaths over 13 weeks gestation are associated with complications of anesthesia (17) or infection. Deaths under 13 weeks gestation are associated with infection and/or hemorrhage (31).

Puerperal Sepsis

Puerperal sepsis occurs in 2.7-5.2% of pregnancies, depending on the region in the world (19). It is frequently Gram-negative bacterial sepsis caused by extension of local infections into the systemic circulation (for example from endometritis, intramyometrial abscess, uterine gas gangrene, or pyomyoma) that causes shock and DIC (20). Sepsis may be difficult to diagnose early on routine blood tests as neutrophilia is a normal pregnancy change.

Venous Air Embolism

Venous air embolism may occur in normal labor, during operative procedures such as termination of pregnancy or cesarean section, secondary to douching, or due to sexual activity.

Venous air embolism requires introduction of a large volume of air into the systemic venous system (at least 150 mL) via distended uterine or cervical veins. This leads to frothing of the blood in right side of the heart which then blocks the pulmonary arteries (17).

Diagnosis of air embolism at autopsy is enhanced by radiological imaging to detect the presence of air in the vasculature and heart and to exclude pneumothorax. Diagnostic changes may be evident on chest radiograph, but can be more readily seen with computed tomography (CT). Imaging needs to be performed as soon as possible after death to avoid decomposition gas artifact, such as gas seen in liver.

At autopsy, the body is opened without incising the neck blood vessels. The inferior vena cava is checked for froth or bubbles. The pericardium is opened and filled with water before opening the right atrium underwater to check for escaping bubbles which indicate the presence of air in the heart (17, 22).

Acute Fatty Liver of Pregnancy

Acute fatty liver of pregnancy (AFLP) occurs in approximately one in 7-15 000 pregnancies (17, 21, 23, 32, 33). It has a 10-20% fatality rate, the higher rates being seen in developing countries (20, 21, 23, 32).

The clinical presentation is frequently of abdominal pain, vomiting, and jaundice. There may be associated renal failure. Diagnosis is complicated by a significant overlap in clinical and biochemical features with the HELLP syndrome (33). Acute fatty liver of pregnancy typically occurs in the third trimester of pregnancy (17, 23, 32), but may develop postpartum (33). Risk factors include primiparity, multi-fetus gestation, and male fetus (23, 33).

The cause of AFLP is unknown but is thought to be due to mitochondrial fatty acid beta-oxidation dysfunction in the fetus – particularly deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) (17, 21, 23, 32-34). A fetus that is homozygous for this autosomal recessive disorder causes placental production of fatty acids and their metabolites, which then accumulate in the liver of the heterozygous mother, having a toxic effect on her liver function (33).

Complications include hepatic failure, severe coagulopathy, coma, and death. At autopsy, the liver is macroscopically soft and yellow. Histology of the liver shows severe centrilobular microvesicular steatosis with inflammation and hepatocyte necrosis. In more severe cases, the whole hepatic lobule may be affected (17). Special stains for lipid, such as oil-red-O, may confirm the presence of fat.

Acute Myocardial Infarction

Acute myocardial infarction occurs in approximately one in 10 000 pregnancies. The main risk factor is high maternal age (over 33 years).

Pathological examination of the heart shows 43% with coronary atherosclerosis with or without thrombosis, 21% with coronary thrombosis alone, 16% with

coronary artery dissection, and 29% of cases with apparently normal coronary arteries (25).

Pregnancy-Associated Spontaneous Coronary Artery Dissection

Pregnancy-associated spontaneous coronary artery dissection usually occurs in the third trimester or postpartum in a previously healthy woman (**Image 5**) (35). It is an important cause of acute coronary syndrome that predominantly affects young patients with no atherosclerotic coronary artery disease (36).

It carries a higher-risk presentation than non-pregnancy-associated spontaneous coronary artery dissection, with patients being more likely to present with ST segment elevation and left main or multi-vessel coronary artery dissection (36). The overall incidence of the disease is likely to be underestimated, as most diagnoses are made at autopsy (35).

Although the pathophysiology of pregnancy-associated spontaneous coronary artery dissection is poorly understood, there are some typical postmortem findings in addition to coronary artery dissection in the absence of atherosclerotic disease (35, 37). Periadventitial eosinophilic infiltrate is present in many cases, although it is unclear whether this may be reactive or causative of medial wall weakness (37). Antemortem blood tests may also demonstrate an elevated eosinophil to lymphocyte ratio (37).

Pituitary Gland Infarction

Pituitary gland infarction in the postpartum patient, can be due to Sheehan syndrome, whereby the pituitary undergoes ischemic necrosis as a result of hypoperfusion from hypotension and blood loss during or after childbirth. Signs of acute necrosis may be noted macroscopically with a grey-red appearance to the cut surface and it may be soft to the touch. Later,

Image 5: Coronary artery dissection (H&E, x25).

microscopic evaluation can demonstrate extensive necrosis with ghost cells, necrotic debris, and inflammatory infiltrate (38).

Anesthetic Complications

Anesthetic complications in the pregnant patient encompass those which may occur as a result of any anesthesia, such as anaphylaxis, aspiration of gastric contents, or intubation complications, including malplacement of the endotracheal tube and damage to the trachea or larynx.

Additionally, there are conditions that are more specific to the pregnant patient, for example iatrogenic pulmonary edema from drugs used to suppress premature labor (especially ritodrine plus betamethasone) (39), bronchospasm in an asthmatic woman secondary to administration of ergometrine (40), and water intoxication following infusion of electrolyte-free, glucose only solutions plus syntocinon (41). The latter is particularly a problem if there is preexisting cardiac disease.

Multifactorial Conditions and Generalized Complications of Direct Maternal Deaths

Hemoperitoneum

Causes of hemoperitoneum include uterine rupture, ruptured subcapsular hematoma of liver (in HELLP syndrome), and ruptured aneurysms, particularly of the splenic artery.

Uterine rupture accounts for approximately 5% of maternal deaths per annum in the USA and has a death rate of about 15% (17). Uterine rupture may be due to trauma, for example during obstetric interventional procedures or secondary to an assault, motor vehicle collision, or fall. In these cases, the site of rupture is often at the fundus of the uterus.

In nontrauma-associated uterine rupture, the rupture is frequently at a site of scarring, for example the lower segment of the uterus through a previous cesarean section scar. The risk of nontrauma-associated uterine rupture is increased in multiparity, with in-

creased maternal age, and following the use of uterotonic drugs such as oxytocin. A study by Miller et al. showed that 142 of 153 cases of nontrauma-associated uterine rupture were related to previous cesarean section (42).

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation occurs most often in the following complications of obstetrics: placental abruption, saline-induced therapeutic abortion, retained dead fetus or products of conception, amniotic fluid embolism, Gram-negative sepsis, and preeclampsia. Placental tissue with tissue factor activity enters or is exposed to the maternal circulation. Clinically, the subsequent rapidly evolving DIC results in severe thrombocytopenia, prolonged prothrombin time and partial thromboplastin time, rapidly declining plasma fibrinogen concentration, and high plasma d-dimer concentration. Disseminated intravascular coagulation causes hemorrhage and shock and can result in death.

Macroscopically at autopsy, purpura are seen and there is evidence of generalized bleeding (43, 44).

Microscopy shows the presence of microthrombi in organs, but particularly in the lungs and kidneys (45, 46). The microthrombi may be confirmed by a fibrin stain, such as Martius scarlet blue.

Thrombotic Microangiopathy of Pregnancy

Thrombotic microangiopathy is the primary or secondary development of microthrombi in blood vessels.

Included under the direct causes of thrombotic microangiopathy of pregnancy are thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) (47).

Secondary causes include preeclampsia/eclampsia/HELLP syndrome, acute fatty liver of pregnancy, systemic lupus erythematosus, and antiphospholipid antibody syndromes.

For definite diagnosis of the etiology, a detailed clinical history is required with antemortem laboratory testing (17, 47).

In the case of TTP, the most common clinical symptoms are neurological, with headache, paresis, speech abnormalities and confusion. Antemortem laboratory testing reveals thrombocytopenia, anemia, and raised lactate dehydrogenase, and creatinine, whilst antemortem urine analysis demonstrates proteinuria and hematuria (47). On postmortem evaluation, TTP microthrombi are widespread and typically affect multiple organs such as the heart, kidneys, skin, and adrenal glands. (47).

In HUS, the classical clinical presentation and laboratory findings involve the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure, with initial symptoms of vomiting and diarrhea and rapidly progressing oliguric renal failure (47). The kidney is the primary affected organ, although thrombosis of small vessels is also commonly found in the colon.

Diffuse Alveolar Damage

Diffuse alveolar damage may occur secondary to a number of conditions complicating pregnancy, such as prolonged artificial ventilation, DIC, sepsis, and amniotic fluid embolism.

Indirect Maternal Deaths

Preexisting maternal diseases that may be aggravated by the pregnant state are listed in **Table 2**.

Cardiovascular Disease and Pregnancy

Pregnancy may cause aggravation of preexisting cardiac or vascular disease, particularly congenital heart disease, inherited cardiomyopathy, ischemic heart disease, valvular heart disease, channelopathies (such as Long QT syndrome), hypertension, and connective tissue diseases with risk of aortic dissection (17).

Aortic dissection typically occurs in the third trimester of pregnancy or postpartum in a woman with an underlying genetic predisposition or known connective tissue disorder such as Ehlers-Danlos syndrome or Marfan syndrome. It is thought that aortic dissection is triggered by a combination of pregnancy-induced hormonally-mediated biochemical changes and the effects of pregnancy-induced hemodynamic stresses on an at risk aortic wall (17).

Incidental Maternal Deaths

Incidental maternal deaths are those which occur from unrelated causes that happen to occur during pregnancy or in the puerperium.

Table 2: Maternal Diseases Associated with Indirect Maternal Death

Cardiovascular disease
Hematological conditions (e.g., thrombophilia states, sickle cell disease)
Primary pulmonary hypertension
Cerebral conditions (e.g., subarachnoid hemorrhage, cerebral infarction)
Epilepsy
Neoplastic disease worsened by pregnancy (e.g., cervical and breast malignancy)
Diabetes mellitus
Infections (e.g., influenza, HIV, tuberculosis)
Chronic liver disease
Autoimmune disorders (e.g., systemic lupus erythematosus)
Psychiatric disease (e.g., suicide risk)

These may be due to accidental causes (frequently as a result of a traffic collision, fall, or drug overdose) (**Image 6**), preexisting advanced neoplastic disorder, or homicide. In the latter case, it should be noted that in some jurisdictions it is a criminal act to injure a fetus by injuring the mother and can result in more serious charges.

The Maternal Autopsy

The maternal autopsy should be a full three cavity autopsy with appropriate ancillary testing including full histopathology and toxicological analysis and other ancillary tests appropriate to the pathological abnormalities found.

The autopsy should be performed as per usual practice for an adult autopsy with special consideration of specific potential lethal complications associated with pregnancy.

As pregnancy may not be suspected prior to autopsy, especially if the woman is in the early stages of pregnancy, the uterus, adnexa, and peritoneal cavity should be examined carefully in all autopsies on women of child-bearing age. For example, this may reveal an ectopic pregnancy which has caused death.

If there has been medical intervention, it is important to look for general complications of any anesthetic or surgical procedure, including esophageal intubation,

Image 6: Uterine rupture after motor vehicle collision with expulsion of fetus into the maternal abdominal cavity. Courtesy of Dr. K Collins, South Carolina, USA.

trauma to the upper airways and/or esophagus, evidence of anaphylaxis to drugs administered, wound dehiscence and/or infection, and trauma to adjacent organs or tissues.

A full clinical history is needed before the autopsy begins. This includes a full obstetric history and antenatal records of the current pregnancy. Cardiotocographic and obstetric ultrasound data should be obtained for expert review if subsequently required. All records relating to any anesthetic or surgical procedures performed should also be obtained, including the drugs given and the dosage.

Prior to autopsy, consideration should be given to radiological examination (plain radiograph or CT) to look for evidence of air embolism.

External Examination

A routine adult external examination should be performed, including evidence of trauma and medical procedures.

Evidence of jaundice (skin and scleral icterus) and hemorrhagic diatheses should be specifically sought, since they may be present in pregnancy-related deaths.

Typical pregnancy skin changes which may be seen include striae gravidarum on the abdomen, thighs, and breasts; hyperpigmentation of the nipples; and linea nigra on the abdomen.

Internal Examination

Routine adult internal examination should be performed, including evidence of trauma and medical procedures.

The fetus and placenta should be examined if they are still *in utero*.

If delivery has already occurred, the placenta should be obtained and examined. Specialist gynecological pathology referral may be requested.

If there is a suspected or possible diagnosis of air embolism the body should be opened without incising the neck blood vessels. The inferior vena cava should be checked for froth or bubbles in the blood. The pericardium is opened and filled with water. The right atrium is then incised under water and checked for escaping bubbles (17, 22).

Specific abnormalities which should be sought to exclude pregnancy-related complications are listed in **Table 3**.

Histopathology

If amniotic fluid embolism is suspected or a possibility, sections should be taken from all lobes of both lungs with special stains performed to detect the components of amniotic fluid (such as a modified Attwood stain and/or immunohistochemistry for cytokeratin and zinc coproporphyrin 1).

The placental bed vasculature of the uterus should always be examined histologically. Normal physiological changes to the spiral arteries in the placental bed of uterus seen on microscopy include replacement of the endothelium by endovascular trophoblast (which spreads to the myometrial segments during the second trimester), fibrinoid change in the arterial walls, and hypertrophy of the radial and arcuate vessels. The basal arteries, however, remain normal.

Examination of the placenta should include sections from the central and marginal areas of the placenta, any macroscopically abnormal areas, the umbilical cord, and the membranes. Chorioamnionitis and funisitis should be specifically excluded.

If there has been development of DIC, microthrombi may be seen in the tissues. These may be highlighted by special stains such as Martius scarlet blue.

Ancillary Tests

If puerperal sepsis is suspected, aerobic and anaerobic blood cultures and swabs should be taken.

DNA specimens may be taken from the fetus and mother (e.g., a blood spot card), particularly in homicides, cases where there may be issues regarding paternity, and for investigation of potentially inherited disorders (such as connective tissue disorders in aortic dissection or coagulation disorders in pulmonary thromboembolism).

CONCLUSION

Maternal deaths can pose a particular challenge to the forensic pathologist and carry significant short- and long-term implications for family members and wider medical and legal practice. The role of the forensic pathologist has an important contribution to wider surveillance and research processes that can contribute to changes in clinical practice, policy, and subsequent changes in maternal mortality rates.

Table 3: Pathological Conditions Which Should be Specifically Investigated on Internal Examination in a Maternal Autopsy

Region of Body	Pathological Conditions to be Specifically Excluded
Head and Central Nervous System	Intracerebral hemorrhage in hypertensive disorders
	Venous sinus thrombosis, particularly the superior sagittal sinus
	Pituitary gland infarction
	Evidence of trauma and/or infection to the spinal cord if spinal or epidural anesthesia has been used
Respiratory System	Evidence of aspiration of gastric contents
	Diffuse alveolar damage (e.g., secondary to severe hemorrhage or sepsis)
	Pulmonary thromboemboli
	Amniotic fluid emboli – rarely seen macroscopically, but may see lanugo hairs, vernix caseosa, and/or meconium
Cardiovascular System	Coronary artery dissection
	Dilated cardiomyopathy (peripartum cardiomyopathy)
	Frothy blood in the heart and pulmonary arteries in air embolism
	Ruptured aneurysms (aorta or smaller arteries)
	Deep venous thrombosis in the legs in cases of pulmonary thromboembolism; if none are present, also check the pelvic and uterine veins
Gastrointestinal Tract	Hemoperitoneum (hemolysis, elevated liver enzymes, low platelets [HELLP] syndrome, ruptured uterus, ruptured aneurysm)
	Perforations of the bowel related to complications of gynecological procedures
	Ileus
	Hemorrhoids are common
Hepatobiliary System	Steatosis of liver (acute fatty liver of pregnancy)
Genital Tract	Uterine rupture
	Tears that may be related to sites of hemorrhage and/or amniotic fluid entry to the circulation – may be in the body of the uterus, cervix or vagina. Ideally examine after fixation as the tear may be small
	Evidence of ectopic pregnancy (usually tubal, although can be at other sites)
	Retained placental fragments in the uterus and/or abnormal placentation
	Retroplacental clot
	Hemorrhagic infarction in uterine leiomyoma

In the USA in particular, recent trends in maternal mortality have demonstrated increases in maternal mortality, which contrast with the overall decrease in maternal mortality in the developed world. With the USA carrying one of the highest maternal mortality ratios in the developed world, the role of the forensic pathologist in maternal deaths is important, despite the overall rarity of such cases.

The purpose of this paper has been to review the clinical and pathological features of common pregnancy-related disorders and to give guidelines for performing an autopsy related to maternal death. Whilst there are extensive documented causes of maternal mortality, the pathophysiology of many maternal conditions remains poorly understood or under-researched and careful postmortem evaluation is necessary.

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