CASE STUDY

Difficult Diagnoses in Maternal Death: The Negative Maternal Autopsy

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Disclaimer
The opinions expressed in this review are my own, and are not necessarily shared by members of the MBRRACE-UK expert panels.

Abstract
A proportion of mothers who die during pregnancy, delivery or some time post-partum, have no clear-cut cause of death despite autopsy examination. Such 'negative' autopsies cause pathologists, and all involved in the mother's care, much concern. They illustrate the frontiers of what is known about why and how critical organs fail, and highlight the variation in the detail to which pathologists investigate maternal deaths. This review is intended for obstetricians, to illustrate the utility and some limitations of autopsy analysis of maternal death.

The major scenarios of maternal death where autopsy reveals nothing or only confusing and subtle abnormal morphologies are considered. These include deaths under general and spinal anaesthesia, pulmonary embolism syndromes (air, fat and amniotic fluid), pre-eclampsia-associated deaths, and cardiac deaths including the SADS/MNH syndrome (sudden arrhythmic cardiac death with a morphologically normal heart).

Key to the resolution of these post-mortem diagnostic problems is complete gross and histological examination at autopsy, appropriate additional analysis of body fluids and, in some cases, DNA analysis. All this to be correlated with the clinical circumstances and – critically – the patient's physiological data available around the time the death. Here, a multi-disciplinary input from experts in obstetrics, medicine, intensive care and anaesthesia is invaluable to narrow down the possible pathogeneses and make as accurate a consensus diagnosis as is possible. A major contribution of the autopsy in such cases to exclude alternative possible clinical pathologies. Newer post-mortem examination techniques, such as cadaveric CT scanning, could prove helpful in the future.

It is likely that there are clinico-pathological syndromes in maternal death that still await formal identification and characterisation.

Keywords: maternal death; negative autopsy; fat embolism; amniotic fluid embolism; pulmonary embolism; air embolism; neuro-axial block; high-spinal block; anaesthesia; SADS; pre-eclampsia; post-mortem CT scanning

INTRODUCTION

Death in pregnancy, delivery and soon afterwards is a common global event, though relatively rare now in high-income countries[1]. The proportion of such deaths that then come to autopsy examination, to determine why the death occurred, varies from none in some regions (where the only available data are subjective 'verbal autopsies'[2]) to more than 80% in the UK[3]. This review explores some problems in maternal death autopsy practice. The focus is on those deaths where there appears to be no visible cause. Real case histories are included to introduce the practical and medico-legal problems in the pathological resolution of such deaths.

First, two illustrative unresolved deaths:

Case 1. A 30 year old healthy primigravid woman went into spontaneous labour at 41 weeks gestation. She delivering vaginally in hospital, without any anaesthetic apart from nitrous oxide/oxygen gas inhalation. Whilst pushing, fully dilated, she collapsed unconscious. Rapid delivery with forceps resulted in a healthy baby. But during the subsequent 80 minutes of unsuccessful cardio-pulmonary respiration, including alteplase thrombolysis administration, she was in PEA (pulseless electrical activity) cardiac arrest. The attending doctors wondered whether she had had a pulmonary thromboembolus (PE) or amniotic fluid embolism (AFE).

The autopsy, performed 5 days later, found nothing. Her BMI was 25. A morphologically normal heart; no pulmonary artery thromboembolism; 3 litres of blood-stained fluid in the abdomen without evident point source (ie agonal ooze); a uterus with small amount of placental membranes but no tears or haematoma; no pelvic or leg vein thrombosis; and a normal brain with no arterial haemorrhage or venous thrombosis. The autopsy tissue histology was also entirely negative: specifically excluded were thrombotic microangiopathy in the kidney; thrombi, amniotic fluid mucin and squamous cells in the pulmonary arterioles (using special stains and immunohistochemistry); and any heart muscle or cerebral pathology.

What is going on here? Discussion of the cause of her death continues, and the aetiologies revolve around a very limited number of known scenarios (primarily cardiac malfunction) plus, disturbingly, the possibility that it is a clinical pathology that we have yet to define, let alone understand. It is in this apparent vacuum that clinicians, doctors, families and, critically, pathologists manoeuvre in the subsequent investigations into the death.

The following death has more possible diagnostic scenarios, involved several expert anaesthetists, intensivists, and pathologists; and caused much collateral damage:

Case 2. The 38 year old mother was induced at 38 weeks gestation because of obstetric cholestasis, and had a Caesarean section under spinal anaesthesia for lack of progress after induction. Anaesthesia required two catheter spinal insertions and two doses of the agent. Delivery followed within 25 minutes, but twenty minutes later, without any clinical prodrome, she went into bradycardia and then cardiac asystole. Full immediate resuscitation commenced with transfer to ITU, but six hours later she died without recovery of consciousness.

Our autopsy found only aspiration pneumonitis, evidently acquired after her collapse. Everything else was, as in the first case, normal, although her BMI was high at 35. It appeared to be an

anaesthetic death. Two expert obstetric anaesthetist reports, commissioned by the coroner investigating the death, were conflicting: one concluded that death followed a high-spinal block causing cardiac arrest, the other that this was amniotic fluid embolism syndrome, and not a high-spinal block (there was no amniotic material in the lungs at autopsy).

There were visits from the Police, asking the pathologist to consider whether the anaesthetist who administered the spinal anaesthesia might have acted negligently or even be liable for a charge of manslaughter. We advised them to stop these enquiries – as did the expert anaesthetists – whilst we concentrated on trying to determine what had happened. The investigating coroner had initiated the Police action following the expert's opinion concerning a possible high-spinal block; the police officers were plainly uncomfortable with the process, not to mention out of their depth.

We later learned of the profound effect this death had on the morale of the maternity unit, and particularly on the anaesthetist. He/she had been suspended from work temporarily, and then had their practice limited; the Police questioning followed. The result was depression and related illness, but he/she had come through with strong support from family, work colleagues and the employing hospital. The final outcome of the medico-legal investigation – which took over a year to complete - was that the cause of death was 'unascertained'.

The problem

It is concerning that in the 21st century, we cannot determine with confidence why mothers can die under close medical observation in hospital. It is different in cases of death in the community, where there are no witnesses and so no full clinical story, and a degree of uncertainty over causation may be inevitable. And – in the second case - the extent of the collateral damage that ensued is striking, as the investigations (medical and criminal), the piece-meal release of reports and expert witness opinions ground on over the following year. This was a classic example of the 'second victim syndrome' in obstetrics, where after a traumatic delivery with severe or fatal injuries to mother or infant, labour unit staff can develop a post-traumatic traumatic stress disorder[4]

Neither of these two deaths was an event that could have been anticipated or prevented by different practice; no one had deviated from standard practice guidelines. Taking the confidential enquiry perspective of seeking remediable factors, what would or could the medical staff do differently the next time? The obstetric scenarios were perfectly standard, ie common. We are left with uncertainty, unhappy hospitals, medical staff who have been traumatised, and two profoundly affected families – not to mention pathologists wondering what they might have missed in the post-mortem investigation.

Fortunately, these two cases are exceptional in that the cause of a maternal death was not resolved satisfactorily at autopsy. Having worked directly on >250 such deaths in England in this millennium, as lead pathologist but also in consultation (having all the records and autopsy histology to review), there have been very few where I really do not know what happened. I also work with the UK confidential enquiries organisation that reviews deaths during pregnancy, delivery and up to a year after – MBRRACE (Mothers and Babies: Reducing Risk through Audits and Confidential Enquires across the UK). MBRRACE-associated multi-disciplinary specialists perform document reviews of all maternal deaths in the British Isles, and there are annual reports, with rolling statistics on the current causes of death.

The point of this activity – to categorise the causes of why mothers die as accurately as possible – is surveillance of current obstetric practice and the production of recommendations on how to reduce their frequency in future (see www.npeu.ox.ac.uk/mbrrace-uk/reports).

In most cases of maternal death reviewed through MBRRACE, where the causes seem as obscure as in the first two Cases presented here, the death investigations were incomplete or badly performed, but nevertheless a shortlist of differential diagnoses can usually be proposed.

The negative autopsy

Autopsy pathologists do not like 'negative autopsies'. They imply a possible combination of ignorance, inadequate investigation and technique on the part of the pathologist, or clinical pathological scenarios leading to death for which we have yet no explanation. None of this is comfortable; moreover, the issue is little discussed amongst pathologists and hardly addressed in the case report literature or general textbook accounts – for what is there to write about when it is 'negative'?

What is a 'negative autopsy'? There are two levels of stringency. First, the gross examination of the body reveals no pathology that can account for the death; plus comprehensive tissue examination by histology, and analysis of body fluids for toxins, alcohol, abnormal metabolism or anaphylaxis show nothing to explain the death.

Secondly, the less stringent version is a cadaver that reveals no evident cause of death on complete gross eyeball examination (but histology and toxicology may identify significant abnormalities).

One practical response is to invent causes for death for which the clinical information and autopsy provide no supporting evidence, in the hope that no one notices; a common example has been to exaggerate the amount of coronary artery atheroma and call the death as due to ischaemic heart disease. Over the years (in the UK at least) this is less common; a greater application of the 'Davies criteria' for more accurately ascribing a sudden unexpected death to coronary artery atherosclerosis,[5] plus dissemination of information on SADS/MNH – sudden arrhythmic cardiac death syndrome with a morphologically normal heart, due in many cases to an inherited cardiac syndrome[6] – have helped tighten up autopsy cardiac pathology reporting.

This review is intended to help obstetricians better understand what can be learned from maternal deaths where there is little or nothing to see at autopsy, and to appreciate some of the limitations of autopsy pathology. The topics discussed in this review are anaesthetic deaths, pre-eclampsia toxaemia (PET), cardiac deaths, and the several pulmonary embolism syndromes.

Table 1. Causes of sudden maternal death around the time of delivery – those with minimal or no abnormal pathology at autopsy are **highlighted**.

Organs and systems	Clinical pathologies
Lung	Thromboembolism
	Amniotic fluid embolism
	Fat embolism
	Air embolism
	Acute asthma
	Sickle cell crisis

	Pulmonary hypertension Pneumothorax
Heart	Structural (muscle, valve, coronary) disease **Supine hypotensive syndrome** **Sudden arrhythmic cardiac death syndrome with a morphologically normal heart (SADS/MNH)** **Eclampsia-related cardiac disease & diastolic dysfunction syndrome**
Brain	Acute haemorrhage (eclampsia or other pathogenesis) Venous sinus thrombosis Epileptic seizure
Systemic	Severe sepsis Acute anaphylaxis Drug toxicity (e.g., cocaine and medicinal)
Anaesthesia	**Spinal (see Table 2)** **General (see Table 2)**
Haemorrhage	Genital tract haemorrhage Artery rupture
Unascertained	all the above excluded, complete autopsy and all clinical records available

Causes of maternal death

Table 1 lists the main clinical pathologies that can result in a maternal death around the time of delivery, derived from the literature and personal experience; it is not a complete list of all the causes of maternal death from conception to weeks after a delivery. The majority of the entities will be identified, and others excluded, by careful, comprehensive gross autopsy and histological examination coupled with appropriate microbiology, toxicology and related analyses of body fluids. The pathologies that remain are more difficult and are highlighted in Table 1.

Deaths under anaesthesia

Maternal deaths directly due to anaesthesia are now rare. In the 1970s in UK, they numbered 10 or more each year,[7] but nowadays there are fewer than one a year (a mortality rate of 0.08/100,000 maternities).[8]

Table 2 indicates the pathological consequences where anaesthesia is considered a factor in causing death – both in general and spinal anaesthesia.[9]

Table 2: deaths associated with anaesthesia – the pathological complications

General anaesthesia	Consequence		Spinal anaesthesia	Consequence
Acute anaphylaxis as immune reaction to induction agents and other drugs	Anaphylactic shock		Neuro-axial/high-spinal block	Cardio-respiratory failure

Gastric aspiration pneumonia	Chemical and infection pneumonia	Dural puncture with loss of CSF	Intracranial haemorrhage; venous sinus thrombosis
Inappropriate extubation	Respiratory arrest	Local sepsis	Meningo-encephalitis
Accidental intubation of the oesophagus	Respiratory arrest	Intravascular injection of anaesthetic agent	Cardiac arrest
Overdose of induction agents	Cardio-respiratory arrest		
Central line placement problems	Haemorrhage; embolism		
Inadequate blood volume replacement	Cardiac failure		
Bronchospasm	Respiratory arrest		
Malignant hyper-thermia	Cardio-respiratory arrest		
Supine hypotension	Cardiac failure		

Amniotic fluid embolism syndrome (AFES) and obstetric haemorrhage are sometimes grouped under 'anaesthetic death in pregnancy', because the events frequently commence whilst the mother is under the care of anaesthetists in the delivery suite, and also because anaesthetists have a major role in intensive care units. However, primary obstetric haemorrhage falls outwith the remit of this review; the fact of it is generally obvious, and the aetio-pathogenesis is usually identified from morbid anatomical lesions that bleed, or from coagulopathy that has a specific investigatory route to resolve its many possible causes (which include AFES), or it is from atonic uterus which unfortunately has no specific pathological features. AFES I regard as distinct syndrome and is considered separately.

In the list of fatal pathologies associated with general anaesthesia, several - supine hypotension, overdose of induction agents, inadequate volume replacement - have no morbid anatomical indicators, and their diagnosis following a negative autopsy, is provided or suggested by review of the clinical and anaesthetic records. Where a reaction to anaesthetic agents is suspected, there is no point in attempting blood level analysis of the possible agents, since no one knows how to interpret the results. Acute anaphylaxis and bronchospasm have some positive features including generalised oedema and observable bronchospasm respectively; and anaphylaxis can be confirmed or excluded by analysis of contemporary mast cell tryptase levels in blood – this analysis is reliable.

Central line placement problems should be evident morbid anatomically, and aspiration pneumonia is obvious histologically. Malignant hyperthermia results in non-specific histologies such as contraction band heart necroses, focal necroses in lung tissue and cerebral petechiae – and is correlated with the mother's temperature records.

Inadvertent malposition of an intubation tube in the oesophagus is uncommonly identified at autopsy, since during cardiopulmonary resuscitation (CPR) this will usually have been identified as the problem and the tube replaced. Reliance here is on the observations of those involved in the

procedure. The next Case history illustrates problems around post-anaesthesia extubation and respiratory difficulties in those recovering from a procedure after delivery:

Case 3. A 31 yr old mother, having her second baby, delivered by Caesarean section under epidural anaesthesia at 39 weeks. Estimated blood loss was 0.5-1 litre. The epidural canula was then removed, but shortly afterwards she began to bleed vaginally. Despite applying the standard treatment protocol, bleeding continued and 3 hours after delivery, she went back to theatre for an examination under anaesthesia (EUA) under general anaesthesia, and some retained placenta was removed; a total estimated blood loss of 2.3 litre.

Muscle paralysis was reversed, and the endotracheal tube removed. Subsequent events were incompletely recorded, in particular there were no oxygen saturation measurements for a period of one and three-quarter hours, during which her ventilations were evidently inadequate and she had a respiratory arrest an hour after extubation. She never regained consciousness and died in cardiac arrest 2 hours later.

The autopsy was negative, apart from ischaemic necrosis of the pituitary (the brain was still histologically normal – it takes about 6 hours of survival or more for hypoxic-ischaemic neurone death to be evident microscopically). The conclusion, that this was inadequate supervision of respiration during the recovery period, was reached after a detailed case review with an expert obstetric anaesthetist.

Death from respiratory arrest in these circumstances leaves few or no pathogenetic clues, and the pathologist is very dependent upon the clinical records' observational statements and laboratory data, supplemented where appropriate by the opinion of an expert anaesthetist. The pathologist's role is to exclude as many of the other possible scenarios that could result in a similar-appearing death.[10]

Spinal anaesthesia for delivery is a normal event now, but rarely results in a death (nerve injuries are much more common).[11]

Case 4. An obese 39 year old woman (BMI = 54) had an elective Caesar section at 37 weeks gestation. Initially thoracic epidural anaesthesia was attempted, but it was ineffective, and 20 minutes later, general anaesthesia was induced. Previously her BP had been 120/49 and pulse 91bpm; these changed to 35/27 and 109; then 55/25/ and 110, at the time of knife to skin. A floppy baby was delivered 9 minutes later (she survived, well); 4 minutes later the mother went into cardiac arrest. As the anaesthetists presumed this was hypovolaemic shock, blood was transfused (ultimately 34 units). CPR continued, massive pulmonary embolism was considered, but thrombolytic treatment was not given; then a hysterectomy was performed because of coagulopathy and uncontrolled bleeding. 90 minutes after the arrest she was put on cardiac bypass. 3 hours later, with fixed dilated pupils, she was declared dead.

Despite all this on-going clinical pathology, the autopsy was 'negative'. The heart was normal (and not enlarged, being 0.28% of total body weight); there was no thromboembolism or amniotic fluid embolism; anaphylaxis was excluded through normal blood mast cell tryptase levels; the kidney did not show thrombotic microangiopathy, and the uterus was normal for a recent caesarean section delivery, with no traumatic lesions in the genital tract.

> The possibility of neuraxial/high-spinal block from epidural anaesthesia was considered in multi-disciplinary discussion and excluded. Close scrutiny of the anaesthetic physiology records showed no measurable effect on lung or heart function: there was no respiratory arrest and the heart rate response to low blood pressure was not impeded. The conclusion was that she died from diminished venous return – the supine hypotensive syndrome caused by a gravid uterus[12] – whilst on her back under general anaesthesia, compounded by obesity.

The supine hypotensive syndrome in this case followed spinal anaesthesia but was actually precipitated by the subsequent general anaesthesia. Two fatal scenarios (Table 2) of spinal anaesthesia where observable and measurable pathology are absent – a negative autopsy - are intravascular injection of anaesthetic agent and neuro-axial/high-spinal block.[9,13]

As with respiratory arrest in the context of general anaesthesia, only the clinical and anaesthesia records can provide the evidence for what actually happened. There is nothing the pathologist can do to directly support or refute the proposal of high-spinal block; there is nothing to see, and nothing to measure (this includes analysis of cerebrospinal fluid (CSF), let alone opening the spinal canal through the vertebrae). Their most useful contribution is to exclude all other possible pathologies that might have occurred. And as in Case 2, the final outcome may have to be a matter of opinion.

Finally, there is a related entity reported – sinus bradycardia and asystole during spinal and epidural anaesthesia[14] – which appears to be unrelated to high-spinal anaesthesia causation. Fortunately, death in maternal anaesthesia from this cause appears to be vanishingly rare[15]; but were that to occur, autopsy pathology would not be able to shed any positive light upon the pathogenesis of the event. However, it has been cited in expert reviews of seemingly inexplicable maternal deaths (including Case 2).
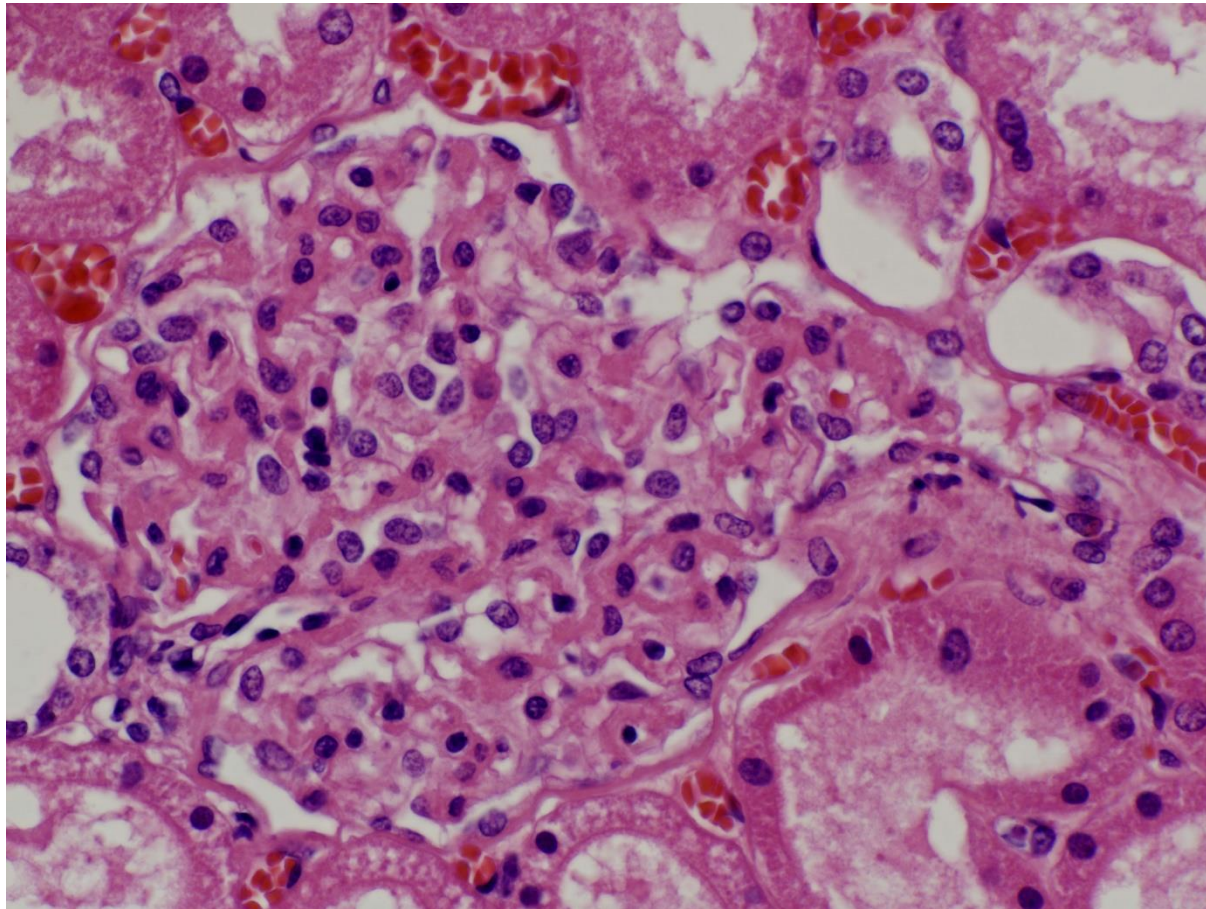
PET and eclampsia

Pre-eclampsia, eclampsia and the HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) – the hypertensive disorders of pregnancy – are well-defined clinically, and the common clinico-pathological features are well known. They include gross intracerebral haemorrhage (due to the hypertension), renal failure (due to the glomerular endotheliosis – Fig 1), pulmonary oedema, placental ischaemic damage, and unique liver periportal vascular lesions – all of which are evident morbid anatomically or histologically. Note that some versions of eclampsia do not manifest gross cerebral haemorrhage, but have widespread petechial brain haemorrhages visible only under the microscope – indicating the importance of all-organ histopathology.

There is a large epidemiological literature on PET/eclampsia and subsequent increased risk of cardiovascular disease, including death.[16,17] There is an increased risk of later hypertension, acute and chronic ischaemic heart disease, heart failure and stroke.[17,18] What there is not is a comprehensive account or review of the cardiac pathology in cases of PET and eclampsia-associated death.

Then there is the diastolic dysfunction syndrome (impaired ventricular filling but normal systolic function), which is particularly associated with PET.[19]

There are difficulties in assessing those women who have suspected PET-related hypertension in the third trimester or after delivery, suffer cardiac arrest and, at autopsy, there is usually nothing specific or definitive to see that accounts for the death at the cardiac level.

Fig 1. Kidney – glomerular endotheliosis in pre-eclampsia. The glomerular capillary endothelial cells are swollen, rendering the loops bloodless (no red cells in the lumens). H&E.

Case 5. A 29 yr old morbidly obese woman developed PET with hypertension and proteinuria at 32 weeks gestation. Despite anti-hypertensive treatment, her blood pressure rose and en route to theatre for an emergency Caesarean section she developed flash pulmonary oedema and cardiorespiratory arrest. Two live fetuses were delivered, and resuscitation was abandoned 45 minutes later.

The autopsy found pitting leg oedema, a large heart (505gm, but only 0.3% of total body weight) with left ventricular thickening, and pulmonary oedema. Histologically, the heart muscle was hypertrophied but otherwise normal; the brain was normal; there was uterine artery atherosis; the kidney showed glomerular endotheliosis. The small lung vessels were normal. The cause of death was acute cardiac failure attributable to PET in association with left ventricular hypertrophy.

There is an uncommon but recognised association of PET with fatal cardiac arrhythmia, as determined from epidemiology.[18] But whether that was the cause of her death, as opposed to the more conventionally acceptable pathogenesis of 'large heart malfunction' is unclear. The next

Case involved the diastolic dysfunction syndrome – not as a pathological diagnosis (there is nothing specific) but from the clinical physiology.

Case 6. A 36 yr old woman had gestational diabetes and hypertension, both treated, and delivered at 39 weeks gestation. At that time, her BP was 170/101, she had leg oedema and proteinuria, ie PET. She was on anti-hypertensive drugs and self-discharged against advice. Three days later she was re-admitted with shortness of breath, worse oedema, dizziness and higher blood pressure. She was treated for suspected pulmonary thromboembolism, but the next day became shocked, acidotic and was in respiratory distress. Intubated she remained haemodynamically unstable although her left ventricular function was normal, and died 5 hours later.

The autopsy found a normal size heart, congested lungs and normal brain. Histologically, the kidney did not show glomerular endotheliosis, but the uterine spiral arteries did have fibrinoid change, a marker of PET; the lungs were congested and oedematous, the heart had only mild left ventricular hypertrophy, a normal right ventricle and atria. From the cardiac echo and physiology data monitored as she was dying, the diagnosis concluded was the diastolic dysfunction syndrome, associated with hypertension. Although by clinical case definition she did have PET at time of delivery, at the time of death this was not evident pathologically in the kidney.

The point of these two Cases is to demonstrate how difficult it can be to establish and categorise why women with PET die, when the expected gross pathological features of intracerebral haemorrhage or liver damage as in HELLP, are not present and it all rests on the clinical story and the autopsy histopathology.

Other cardiac and cardiovascular diseases

In the UK and USA, cardiac and cardiovascular deaths are the leading cause of maternal death.[3,20,21] Within that category are many pathologies that are evident with agreed case definitions, those that have more subjective case definitions and may overlap with normal heart structure (eg the hypertrophied hearts), and the entity of sudden arrhythmic cardiac death syndrome with a morphologically normal heart (SADS/MNH) where by definition the heart is normal. For several of the diseases, the utility of genetic analysis for characteristic abnormalities is increasing[6]. The diseases are categorised in Table 3.

Table 3. Cardiac and cardiovascular pathology entities in maternal death[3] – the range includes evident abnormality but overlaps with normal heart structure.

Pathology standard and evident	Pathology characteristic and genetic analysis helpful	Pathology subjective with imprecise or no standard case definitions; genetic analysis under investigation	Normal heart, no pathology; genetic analysis may be helpful
Dissection of the aorta	Hypertrophic cardiomyopathy	Hypertension without PET	SADS/MNH – sudden arrhythmic

			cardiac death syndrome, morphologically normal heart
Ischaemic heart disease due to coronary atherosclerosis	Arrhythmogenic right ventricular dysplasia	Hypertension with PET	Ventricular tachycardia syndromes (diagnosed on ECG)[24]
Ischaemic heart disease due to coronary artery dissection	Idiopathic restrictive cardiomyopathy	'Idiopathic' left ventricular hypertrophy	
Valvular disease		'Idiopathic' left ventricular hypertrophy with interstitial fibrosis	
Congenital heart disease		Dilated cardiomyopathy	
Myocarditis,		Peripartum cardiomyopathy	
Pulmonary hypertension		Obesity cardiomyopathy	

As this review focusses on negative autopsy maternal deaths, this cardiac overview is brief and highlights the uncertainty in case ascertainment in the more difficult areas.

Left ventricular hypertrophy (LVH) is a common cause feature of cardiac death, sudden or with prolonged heart failure, and the hearts are usually enlarged relative to body mass (the normal ratio is <0.5% total body weight) and there is usually left ventricular wall thickening. But ascertaining is pathogenesis is in practice often subjective rather than evidence-based. Dilated cardiomyopathy (DCM) is notoriously imprecise for categorisation. It is characterised by ventricular chamber enlargement (but not always hypertrophy) and systolic dysfunction in the absence of abnormal loading conditions (hypertension, valve disease) and coronary artery disease. Pathogenetically, most cases are 'idiopathic', but alcohol, virus infection (with or without evident myocarditis), previous hypertension and autoimmune disorders, let alone genetic associations, are all possible.

Peripartum cardiomyopathy (PPCM), whose pathogenesis is obscure but whose morphology is a non-specific dilated cardiomyopathy, is a special case in its specific association with pregnancy. In practice, few fatalities from PPCM come to autopsy because the diagnosis has been made clinically and the clinical deterioration is slow rather than rapid. The case definition is clinical and chronological (not pathological), with the usual exclusion criterion of no other cause of left ventricular systolic heart failure being found. Unfortunately for pathology research studies, in-life biopsies of PPCM are rarely undertaken.[22]

Morbid obesity produces many practical problems in obstetrics and an increased risk of cardiovascular disease. The pathologies include the hypoventilation-pulmonary hypertension syndrome, systemic hypertension, diastolic ventricular dysfunction, dysrhythmias, increased risk

of thromboembolism, and the uncommon so-called 'obesity cardiomyopathy' (OCM). There is a proposal to standardise OCM pathologically to distinguish it from ordinary LVH and normal structure, requiring the following features:[23]

- Increased heart weight
- Left ventricular or biventricular hypertrophy; +/- small foci of fibrosis but not extensive ischaemic fibrosis
- Dilatation of atria and ventricles
- Marked fatty infiltration of the right ventricle, but without fibrosis (which is a characteristic of arrhythmogenic right ventricular dysplasia)
- Exclusion of coronary artery disease, myocarditis, acute infarction and other clear alternative causes of death

Overall, there is such variation among pathologists as to how this group of heart diseases are depicted in autopsy accounts, that national surveys of maternal cardiac pathology inevitably present different proportions of the various categories.

Until more systematic and rigorous morphological descriptions of these hearts, in association with systematic search for possible underlying pathogens and genetic abnormalities are undertaken, progress in better categorising these difficult clinical pathologies will be slow. It is not surprising that 'ventricular disease not otherwise specified' remains a common default diagnosis in cardiac maternal death.

SADS/MNH

Then there is the syndrome currently labelled SADS/MNH: sudden arrhythmic cardiac death syndrome with a morphologically normal heart. This entity has become recognised over the last two decades as it became irrefutable that people – including pregnant and post-partum women – die suddenly from acute arrhythmic heart failure with no evident pathological or toxic cause, usually after an episode of ventricular fibrillation. In retrospect, many such patients had a history of similar sudden unexpected deaths in the family and suffered from blackouts.

Interestingly, as recently as 2012, a review of cardiac disease in pregnancy by obstetric physicians made only passing mention of SADS/MNH and none of 'undetermined cardiac death'.[24] Making the diagnosis in life is potentially life-saving for the patient as drug therapy and/or pacemaker insertion is the treatment; it also prompts screening of family blood relatives in case they have the same condition, for it is often an inherited heart disease. Genetic analysis of patient DNA can identify long QT or Brugada syndrome in a small proportion of subjects[6] – but hopefully the proportion so identified as genetically determined will increase with more intensive research.

In the UK at least – for it appears only rarely in other nations' reviews of the causes of maternal death[25] – SADS/MNH is relatively common. In the triennium 2009-14 it was the second commonest cause of all maternal deaths, as well as the commonest cause of cardiac death (31%)[20].

In 2015-17, it was the second commonest type of cardiac death, after the heterogenous group of cardiomyopathies listed in Table 3.[3]

Case 7[3]. A 36 yr old woman with known Long QT syndrome-2 was advised by her cardiologist to stop her beta blocker during pregnancy. This erroneous advice was not followed and she gave birth uneventfully. However, she discontinued the beta-blocker postnatally and although advised to restart after admission for an episode of syncope, she was found dead at home a few months later. The autopsy was negative, the heart of normal size and morphology. On full toxicology screen, no beta-blocker was detected in blood assays at post-mortem.

In the previous triennial survey[20], another long QT-associated SADS maternal fatality was identified by DNA analysis of the mother's spleen taken at autopsy.

Women with long QT syndrome are particularly at risk of ventricular arrhythmia and sudden death in the postnatal period. This increased risk extends for nine months postpartum and is reduced by beta-blocker treatment. Women with LQTS-2 type appear to be at the highest risk of sudden death in this postpartum period[26].

In most of SADS/MNH deaths in the 2015-17 enquiry period, splenic tissue was retained at autopsy which can be used for subsequent DNA analysis and potential family screening. Also many of the autopsy hearts had been referred to an expert cardiac pathologist for definitive examination. Like unexpected deaths in epilepsy (Table 1), SADS/MNH is a diagnosis of exclusion.

So: should we apply the diagnosis of SADS/MNH to all maternal deaths where the autopsy is entirely negative and there is no toxicological cause? In the UK, the answer is, to an extent, yes. If the circumstances include witness observation of sudden cardiac arrest, ventricular fibrillation on ECG, a family history of similar death and a personal history of previous blackouts – then there is no debate: this is SADS/MNH. If DNA analysis of the mother, or evaluation of blood relatives, can demonstrate a gene abnormality known to be associated with the syndrome, then the case is complete. That 'pure' scenario is uncommon, and decisions are made according to how close to it a particular death comes; fundamental is the rigorous exclusion of alternative causes of death.

Attributing such deaths to SADS/MNH has the positive function of focussing attention not only on practical measures in the community to manage cardiac arrest, but also on research endeavours to understand such deaths and their possible familial linkages. This is a scenario that applies to the general population as well as to mothers. And it reminds us to constantly think whether there might be as yet undescribed pathogeneses of maternal death and how we might identify them.

The pulmonary embolism syndromes

In high-income countries, venous thromboembolism (VTE) is usually listed in the top 3 causes of maternal death. Whilst we know a great deal about the risk factors, presentation, management and prevention of pulmonary thromboembolism, this is nearly all based upon direct clinical observations during the pregnancy. Unfortunately, much of the mortality happens out of the blue in the community, and the mothers die outside hospital or shortly after emergency admission, at

which point the diagnosis becomes a pathological one. Usually this is a straightforward morbid anatomical issue to address.

Venous thromboembolism and its treatment with thrombolysis

A recurring question in maternal autopsy practice surrounds the investigation of women suspected to have died of significant venous thromboembolism, have been given thrombolytic therapy, but have then died within the next hour or so – and the autopsy shows no thrombi in the pulmonary artery. Can the pathologist be certain there was no major thrombus? Could the thrombolytic drug have dissolved a thrombus, rendering it invisible to detection?

The first question is resolved by careful dissection of the entire pulmonary artery tree, bearing in mind that to cause a sudden cardiorespiratory arrest, a venous thromboembolism needs to be large enough to locate in the main pulmonary trunk or one or both main pulmonary artery branches, or in most of the lobar pulmonary arteries. Histological demonstration that a clot is a true thrombus, and not a post-mortem coagulation clot, is highly recommended in maternal pathology work, where the fact and the chronology of venous thromboembolism is frequently the subject of litigation: when did the thrombosis and embolism processes start, and why was it not anticipated or prevented?. Sampling the thrombus itself, its adjacent lung arteries and its actual or presumed venous location can generally indicate with some precision how long the thromboembolic process has been going on for.

The second question is more difficult. To my knowledge there is no literature, experimental or observational, on the rate at which thrombolytic therapy impacts upon large pulmonary thromboemboli to dissolve them. Catheter-directed thrombolysis is clinically noted to be effective in 'massive' and 'submassive' pulmonary thromboembolism.[27] But I wonder if we are not looking at different types of pulmonary embolism. From my own observations of general, as well as maternal, autopsy work on patients who have been thrombolysed, where the times of therapy and death may be more prolonged than in emergency maternal situations, I have no doubt that a few hours exposure to a thrombolytic drug has minimal impact on the size or adhesion of a large thromboembolus (1-2cm in diameter). Thus in my opinion, if a pathologist finds no thromboembolism in a maternal sudden death where it was expected by the treating doctors, it was not there. More research on the patho-morphological impact of thrombolysis would be useful.

Air embolism

Venous air embolism (VAE) is said to occur in 10-97% of women undergoing caesarean delivery,[28] but is rarely fatal. Even rarer are pregnant women who die from VAE following criminal or therapeutic abortion. The lethal volume of air introduced is greater than 200ml (3-5ml/kg body weight); it arrives in the right ventricle and produces an air lock, with resulting reduction in cardiac output and cardiovascular collapse.[29] In case reports it is often a diagnosis of exclusion.[30]

The diagnosis of VAE in life involves imaging, arterial catheterisation, and Doppler studies,[28,31] and it is difficult at autopsy.[10] Whole body X-ray or (better) CT scan can show significant air volume in the heart (right atrium and ventricle) and great vessels. If that is not available, using a knife the pathologist opens the right ventricle, with the heart in situ and the opened pericardium previously filled with water: air bubbles appear in quantity if there been a large venous air embolism. The old adage that seeing the superior meningeal vessels of the brain filled with air

bubbles indicates air embolism is false: that is an artefact caused by the negative pressure of opening the skull.

In the UK, deaths from VAE rarely appear in the annual reports. Given the difficulty in establishing the diagnosis at autopsy, it is possible that such deaths are under-counted. The following Case exemplifies how it may have to be a diagnosis of exclusion when women who have collapsed, rather than dying rapidly, are cared for in intensive care units for some time before succumbing.

Case 8. A 31 yr old woman had a caesarean section under spinal anaesthesia at 38 weeks of gestation. While the uterus was being closed, she became breathless, with a respiratory arrest, followed by cardiac arrest. She survived for three days with hypoxic-ischaemic encephalopathy before dying. Apart from the brain damage, the autopsy was entirely negative.

The diagnoses listed in Table 1 were considered in a multidisciplinary consultation, and all but air embolism and fluid overload syndrome were discarded. Further examination of fluid balance and drug charts indicated no fluid overload. Although no air embolism was seen at autopsy – and would not be expected, given that the air would have been absorbed during the three-day delay between collapse and death – the final diagnosis of exclusion, on balance of probabilities, was air embolism.
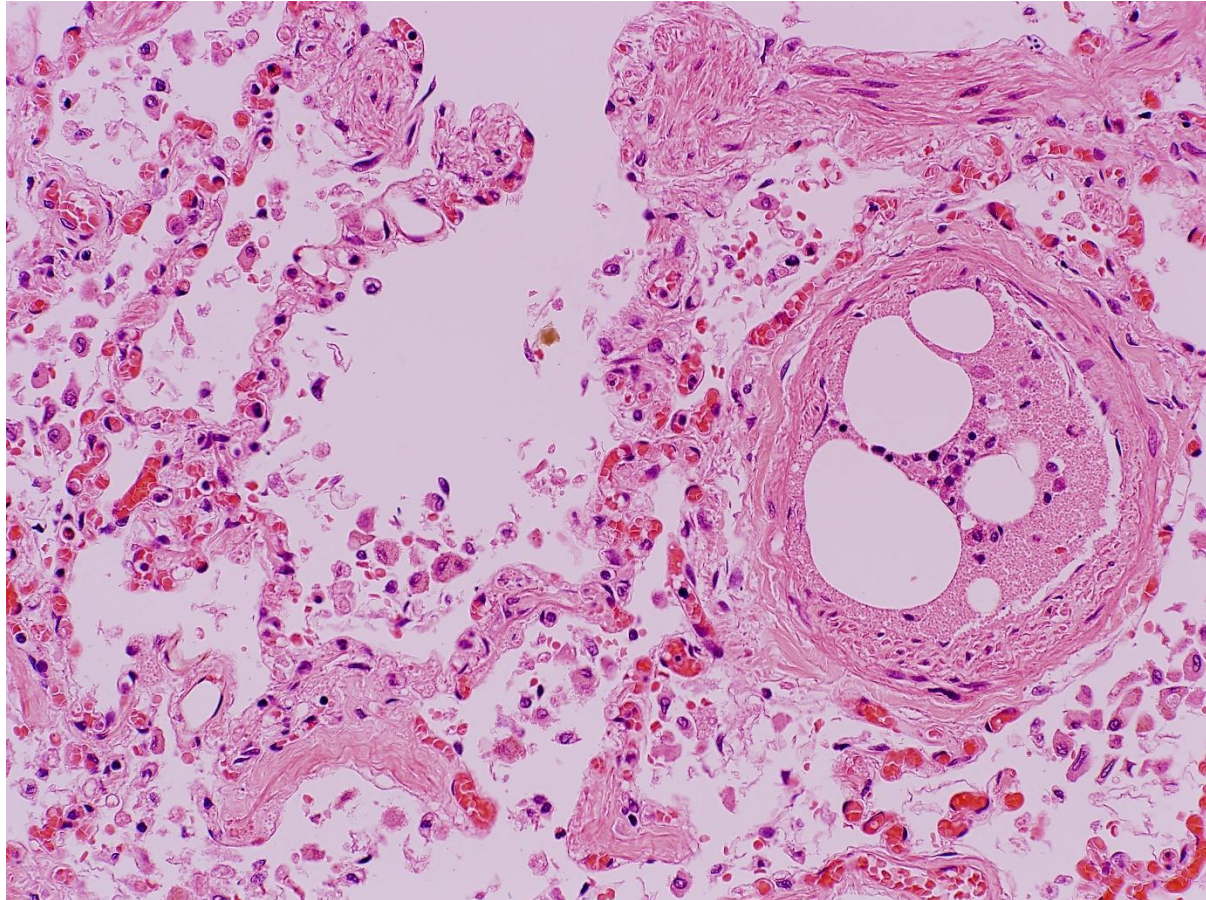

Fat embolism

Is peri-delivery fat embolism a genuine clinico-pathological entity? It can occur in pregnant women with sickle cell disease who necrose their bone marrow, following trauma, and rarely in acute fatty of pregnancy.[32] The following Case history illustrates how confusing and difficult cases without clear pathology can be.

Case 9. A 36 year old woman was at term in her first pregnancy. Her platelet count was chronically low at 90×10^9/L for reasons never identified, and she had intermittent hypertension. For breech presentation, she had a Caesarean section under spinal anaesthesia without problems. The baby went to neonatal care for suspicion of sepsis, so she remained in hospital. Fifty hours after delivery, having being seen sleeping in the ward at 6.30am, she was found dead two hours later. Vigorous cardiopulmonary resuscitation (CPR), which included thrombolysis, was unavailing.

At autopsy, the heart was grossly normal as were all the other organs. A toxicological screen found nothing abnormal. The histology, looked at by several pathologists, was reported as the lung showing multiple thrombi and fat embolism, but no amniotic squames; the brain histology showing multiple white matter petechial haemorrhages; and the liver having focal hepatocyte necrosis but no steatosis. The original conclusion was disseminated intravascular coagulation, probably the result of amniotic fluid embolism.

Because a claim for clinical negligence was lodged against the hospital (the relatives believed that the HELLP syndrome might have been the cause of death), expert reviews of the case management and autopsy pathology were commissioned. An expert obstetrician correctly dismissed the diagnoses of HELLP syndrome and amniotic fluid embolism syndrome on clinical, laboratory data and chronology grounds; but concluded that since there were fat emboli in the lungs, this death was probably the 'perinatal fat embolism syndrome'.[33] However, expert pathological review found no liver pathology; no amniotic fluid embolism nor any thrombi in the lungs; and the reported brain haemorrhages were carry-over histological artefacts. The fat emboli in small lung vessels

were confirmed, but attributed to CPR (Fig 2). The final conclusion - accepted by all the interested parties - was that this was probably a cardiac death, and as a diagnosis of exclusion, attributable to SADS/MNH.

Fig 2. Lung – fat embolism from cardiopulmonary resuscitation effect. The arteriole has fat globules and some surrounding bone marrow; to the left are capillaries with empty lumens, indicating circulating fat globules. H&E

Fat embolism commonly occurs during cardio-pulmonary resuscitation (CPR) as ribs are fractured. In patients autopsied after dying of non-traumatic medical causes, it is almost universally seen microscopically in the autopsy lungs of those unsuccessfully resuscitated, and similarly not seen in the lungs of those who were not resuscitated.[34] Thus, true pregnancy-associated pulmonary fat embolism syndrome – if it exists at all – is rarer than deaths from SADS and amniotic fluid embolism with which it can be confused. I would suggest that it should never be considered as a cause of death outside the scenarios of non-CPR-related trauma, fatty liver, and sickle cell disease.

Amniotic fluid embolism

Finally we must address the autopsy pathology and diagnosis of the amniotic fluid embolism syndrome (AFES), which is the 9th commonest cause of maternal death in the USA,[21] and in the

UK fluctuates in mortality rate from 0.26-0.68 per 100,000 maternities[3]. Although the autopsy is not generally 'negative' in AFES, as there are amniotic squames and mucin (AFE material) to be seen in the lung arterial system, it is important for the following reasons:

1. AFES has a clinical case definition, which varies from region to region,[35,36] and there are no reliable laboratory tests for it in life;
2. Its pathogenesis is still obscure and controversial (I will not delve into this aspect here);
3. The autopsy identification and confirmation of AFE is notoriously difficult, it being easy both to miss and to over-diagnose (eg Case 9);
4. It has a high mortality, estimated at 20-30% according to case definition and local maternal death investigation practices;
5. It is a major source of clinical negligence litigation in deaths from post-partum haemorrhage, because of diagnostic confusion over its actual presence (or not.[37] AFES is seen as a valid defence against accusations of professional negligence, it being an event out-of-the-blue with variable outcome despite adequate intensive care.[38]

Despite the variation in case definitions (in UK, there is no time frame specified from delivery to clinical onset,[36] whereas in USA and France, it is within 30 mins[35,39] – whilst there are case reports of it occurring later, up to 4 hours post-delivery[40]), the clinical features are familiar. The onset is with sudden cardiac and respiratory malfunction leading to collapse, often with a premonition of catastrophe on the part of the mother. There is a coagulopathy with uterine bleeding and abnormal clotting blood tests; this bleeding can also be the first manifestation of AFES. Interestingly, thrombotic microangiopathy is never seen in the renal glomerular capillaries in AFES, despite the usual term 'disseminated intravascular coagulation' being applied to the coagulopathy. Seizure is a less common primary presentation feature.

As demonstrated by published data on the mortality rate of AFES, ranging from 20-30%, the majority of cases are diagnosed clinically, not pathologically. Only a small proportion are subjected to autopsy, where there is published consensus that AFE material should be identified in the lung vessels, whereas it is not so found in women who have died of other causes. Conversely, in-life blood cytology studies have shown the presence of fetal squames in the circulation of pregnant women who are not experiencing the AFES.[41] However, we have noted a few indubitable examples of typical AFE material in lung arterioles - but, critically in very small, almost missable quantities, using special stains to highlight the cells histologically - in a few women who have died from different pathology. The next Case is a much grosser example of this phenomenon:
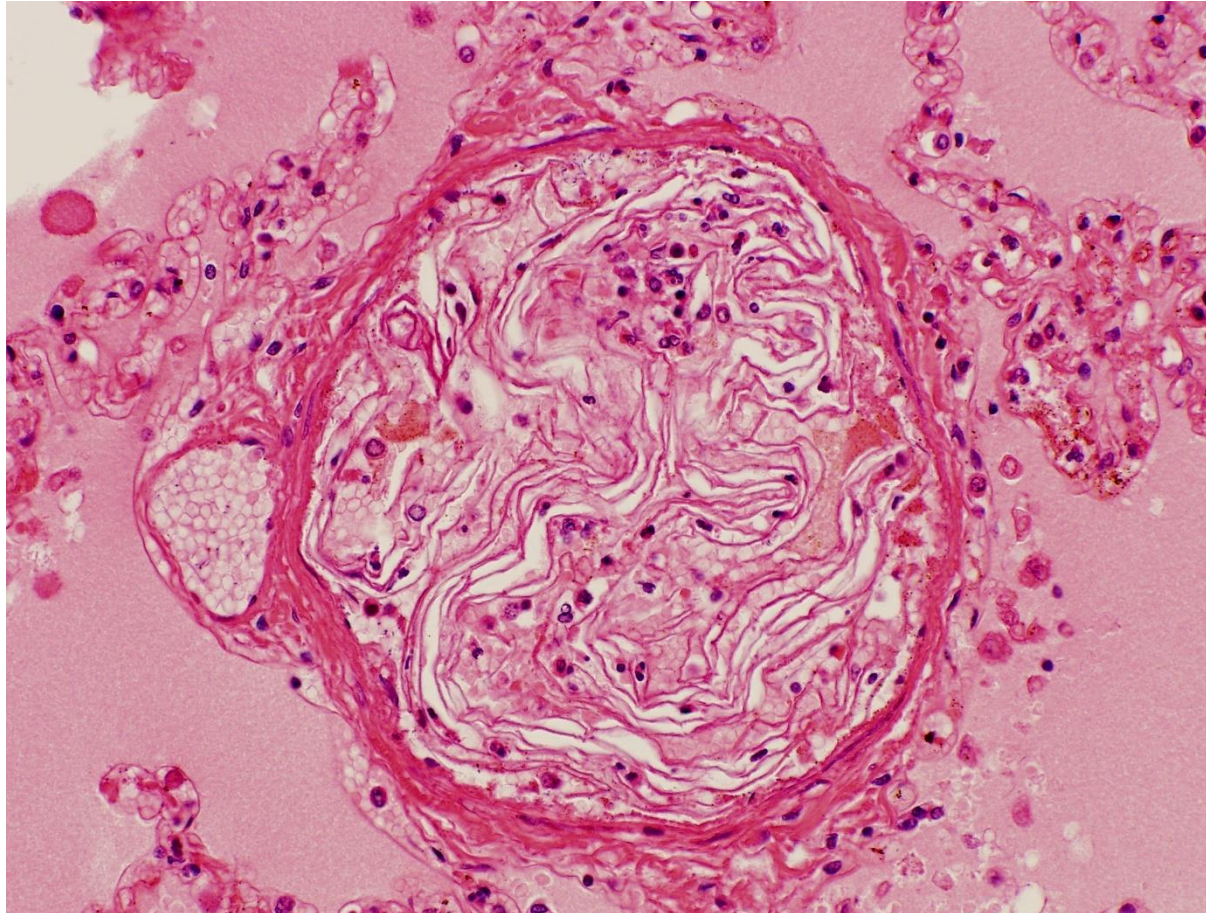
Case 10. A 28-year-old primip reached 39 weeks of gestation with no antenatal medical problems. She had not started labour and her membranes were not ruptured. She was witnessed to collapse at home during an agitated phone call to her ex-partner, then stop breathing and become pulseless. A bystander commenced CPR and this was continued by the ambulance staff. They found no pulse, and the ECG trace showed the woman was in ventricular fibrillation.

A defibrillator was used to deliver one shock, but this did not restore the heart rhythm and she was asystolic thereafter. The woman was declared dead after more than one hour of intensive resuscitation which included a perimortem caesarean section.

Lung histology taken at autopsy found massive quantities of amniotic fluid material in the pulmonary arterioles (Fig 3). The heart was entirely normal, as was the brain.

In this scenario, there was clear evidence of acute cardiac arrhythmia; but she was not in labour, without rupture of membranes or interference with the uterus prior to her collapse, and no evident prodromal symptoms indicative of amniotic fluid embolism syndrome (AFES). Therefore, it was decided that the death was caused not by AFES but sudden cardiac death syndrome (SADS).

Fig 3. Lung - amniotic fluid embolism. The pulmonary arteriole is stuffed with embolised angular squamous cells. H&E

It would be easy to declare this death as due to AFES; after all the pathology was positive and that is a component of some but not all case definitions of AFES: Clark omits it[35], whilst Knight includes it[36]. But the scenario of the death did not fit.

Table 4: Amniotic fluid embolism (AFE) scenarios and autopsy evaluation of the AFE syndrome (AFES).

Clinical scenario	Lung pathology	True AFE syndrome?	Not the AFE syndrome?
Typical for AFE syndrome	AFE material in circulation	YES	And there is no alternative compelling pathological diagnosis

Some features of AFE syndrome	No AFE material seen	LIKELY. Depends on: stringency & sensitivity of the histological examination; whether there is a more compelling and uncontroversial pathological cause of death	YES If there is a more compelling and uncontroversial pathological cause of death
No features of AFE syndrome	AFE material in circulation	UNLIKELY Is there a more compelling pathological cause of death?	'Pseudo-AFES' due to cardiopulmonary resuscitation whilst fetus still in utero; exhaustive histological examination can reveal small amounts of AFE material where other obvious cause of death is present
Uterine haemorrhage without cardio-pulmonary collapse	AFE material in circulation	POSSIBLE Exclude traumatic causes for haemorrhage. Correlate the clinical data, lab haematology data, the chronology of delivery, haemorrhage and resuscitation	Could be resuscitation effect or 'normal' small amount of AFE in circulation
Abdominal trauma followed by collapse[42]	AFE material in circulation	YES	Check that a more compelling traumatic cause of death is excluded.

Table 4 shows an approach to establishing or refuting the diagnosis of AFES in difficult cases that come to autopsy. Necessarily there has to be a complete autopsy with histological examination of all organs to exclude alternative diagnoses, with at least one block of lung tissue taken from each of the 5 lung lobes for histology. Blood mast cell analysis is often performed, and sometimes, but not usually, the level is raised in cases of AFES (but again there are confounding factors - cardiopulmonary resuscitation itself causes release of the enzyme from mast cells).

Medicolegally, the commonest issue is whether the AFES caused a fatal obstetric haemorrhage versus whether the haemorrhage was initiated by genital trauma or was a sub-optimally managed spontaneous haemorrhage from an atonic uterus. Meticulous pathological examination, correlated with precise chronology of the clinical events and changing laboratory results, should in most cases result in rational consensus.

Maternal autopsy futures

So far I have illustrated what is essentially the current practice in the UK, where it would appear that maternal deaths are more thoroughly and systematically examined, and discussed on a national scale, than in any other country.[43] The high autopsy rate, the annual production of an analytical report with recommendations on how further to reduce mortality, and constant encouragement to improve the quality of the autopsies undertaken, are widely appreciated by obstetricians. Other nations do things differently, and may achieve a less accurate overall perspective on what is happening in maternal death and changes in outcomes over the years.

However, there is a global trend toward fewer medical autopsies, as opposed to forensic examinations - which are not the concern in this review, necessary though they are when mothers are the victims of trauma etc. This is for many reasons, including shortage of skilled pathologists to perform them, costs, and societies' dislike of the autopsy, not to mention clinical hubris. A consequence has been to seek alternative non-invasive post-mortem examination techniques, one of which is post-mortem cadaveric CT scanning[44] – PMCT. Unquestionably, PMCT can identify many pathologies, and (when coronary angiography is added in) can thus diagnose several of the maternal conditions that cause death: eg

- Ischaemic heart disease
- Aortic dissection
- Intracerebral haemorrhage
- Air embolism[31]

It cannot visualise venous thromboembolism or the complex range of heart muscle lesions, and certainly is of no use in identify sepsis, pulmonary hypertension, the eclampsia syndromes that do not involve cerebral haemorrhage, AFES, and so on. Some women who die in pregnancy and after in health care settings will have had CT scanning as part of diagnostics. Ideally, all those who have not, and all those who die in the community should have a PMCT scan as part of the post-mortem investigative process. This will resolve some causes of death rapidly and, as a general principle, it always enables the pathologist performing a subsequent autopsy to do a higher quality examination.

Available skilled pathology and PMCT are still the preserve of high- and some middle-income countries, and are generally lacking in the low-income countries where the majority of maternal deaths take place[1]. The only recourse there is a 'verbal autopsy'[2], but little can be expected in terms of accurate detail on causes of death that are usable on a local scale. Experience of maternal autopsy work does not lend confidence in the accuracy of usual global proportional cause of death data that WHO provide. There is more to it than just "severe bleeding, indirect, infection, unsafe abortion, eclampsia, other direct, and obstructed labour". And that information is what the autopsy could provide.

Finally, considering autopsy practice in high-income countries, one issue that has become more prevalent is the impact of intensive care (ITC) for mothers when they have collapsed. As a cornerstone of modern medicine, ITC increasingly takes in ill mothers and keeps them alive. This is excellent, but there is a drawback: if the mothers do eventually die and the actual pathological reason that necessitated their admission to ITC was not clear at the time they entered, then the autopsy rarely identifies what the critical event was, if some time – more than a few days – has

passed since admission. The event causing the collapse has resolved or become overlain by the impact of ITC interventions. This is a general principle, applying to all patients who die in ITC.

Conclusions

I have not included discussion of rarer causes of death in pregnant women that we have encountered, which occur not necessarily at the time of delivery, and where there is little to observe at autopsy: the solution to the diagnosis comes from careful evaluation of the clinical story, systemic analysis of autopsy tissues and body fluids and exclusion of alternative diagnoses. These include:

- diabetic dead in bed syndrome[45]
- vagal nerve inhibition of heart rhythm caused by goitre
- polyvinyl alcohol (PVA) particle pulmonary embolism, following uterine artery embolization[43]
- systemic lupus erythematosus and anti-phospholipid syndrome

The main conclusion is that only with full autopsy examination, and multi-disciplinary expert input where necessary, can the difficult, apparently negative-autopsy deaths of mothers in pregnancy and delivery be resolved. Moreover, as the average age and body size of mothers increases, inevitably the clinical pathologies that can happen during pregnancy and delivery become multifactorial and more complicated. To maintain progress in refining our knowledge of why and how mothers die and so help reduce the rates of maternal death, we need more of the quality control measure of thorough and systematic autopsy examination, not less. This, coupled with advances in what we can measure and evaluate in life, will improve maternal health care. National large-scale registration databases with expert input into categorisation are highly recommended.

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