

Are Maternal Deaths on the Ascent in Singapore? A Review of Maternal Mortality as Reflected by Coronial Casework from 1990 to 1999

G Lau, *FAMS, FRCPath, DMJ (Path)

Abstract

Introduction: In Singapore, published maternal mortality rates (MMR) over the last decade (1990 to 1999) have been so low (0.0 to 1.0 per 1000 live births and still births) as to imply that maternal deaths are rare to the point of being non-existent in some years. This inference is counterintuitive, and earlier studies on maternal mortality, amniotic fluid embolism (AFE) and pulmonary thromboembolism (PTE) have also suggested otherwise. Accordingly, local trends in maternal mortality warrant further examination. **Materials and Methods:** A descriptive and comparative study, comprising a clinico-pathological review of maternal deaths, for which autopsies were conducted by the Centre for Forensic Medicine, during a 10-year period from 1990 to 1999. The annual necropsy-based, MMR (estimated MMR), as well as the prevalence of maternal deaths during this time, were estimated with the aid of the relevant, published demographic data on live births and still births. These were compared with the corresponding rates calculated (calculated MMR) from raw demographic data on maternal deaths classified as such in the published data. **Results:** Coronial autopsies were conducted on a total of 51 cases of maternal death, of which 33, 17 and 1 were direct, indirect and fortuitous deaths, respectively. The annual, estimated MMR ranged from 0.4 to 1.8 per 10,000 live births and still births. The estimated MMR was twice as high as the calculated MMR and a statistically significant upward linear trend was demonstrated for the former ($P = 0.046$). AFE (16/51) and PTE (10/51) were the two most common causes of maternal death; their corresponding cause-specific, 10-year prevalence being 0.33 and 0.21 per 10,000 live births and still births, respectively. There was apparent clustering of the cases of PTE during the earlier part of the last decade (1990 to 1995), corresponding to a statistically significant, upward trend in its overall necropsy incidence during that time ($P = 0.019$). Cardiovascular and pulmonary disorders constituted the bulk of indirect deaths (13/17), while antenatal suicides accounted for 3 of these deaths (0.06 per 10,000 live births and still births). **Conclusions:** This was an upward trend in MMR, as reflected in coronial casework, over the last decade. It would appear that the local, estimated (direct and indirect) maternal mortality prevalence compares favourably with the MMR reported in developed countries. The apparent rate of AFE was no less than 4 times higher than that reported in the United Kingdom, while the maternal mortality rate from PTE was at least as high. Allowing for the possibility that such deaths were under-reported, the actual annual MMR and 10-year prevalence could be appreciably higher than the estimates presented here. There may well be a case for the establishment of a comprehensive database of maternal deaths, that is updated continually and contemporaneously, in Singapore.

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Key words: Amniotic fluid embolism, Coronial autopsies, Direct and indirect deaths, Estimated maternal mortality rates, Prevalence, Pulmonary thromboembolism

Introduction

It is said that, worldwide, over half a million maternal deaths occur annually.^{1,2} This might well be a conservative estimate, given the difficulties inherent in collecting the relevant data, compounded by the under-reporting and misclassification of such deaths.¹ It would appear that, despite international initiatives advocating safe motherhood, such as the Nairobi Conference held in 1987,²⁻⁴ data collected by the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) indicate that obstetric disorders remain the leading cause of death (in approximately 16% of cases) among women of child-

bearing age, far exceeding the death rates for tuberculosis, suicide, war injuries, traffic accidents, or even acquired immunodeficiency disease.^{2,5,6}

Apparently, much of what has been described as a neglected tragedy⁷ is played out in developing countries, where approximately 98% to 99% of maternal deaths occur; these being largely due to peripartum haemorrhage, dystocia, eclampsia, infections and complications of induced abortions.^{1,7} This is reflected by the fact that while maternal mortality ratios in most major developed nations tend to range from 10 to 15 deaths per 100,000 live births, the corresponding figure for the developing world (especially

* Consultant Forensic Pathologist and
Deputy Director, Centre for Forensic Medicine
Health Sciences Authority

Address for Reprints: Dr Gilbert Lau, Centre for Forensic Medicine, Health Sciences Authority, 11 Outram Road, Singapore, 169078.
E-mail: Gilbert_LAU@HSA.GOV.SG

sub-Saharan Africa, much of Asia and Latin America) is in the order of 200 to 1000 per 100,000 live births (that is, some 10 to 100 times higher) and even exceeds the respective infant mortality rates.^{1,7,8} Nevertheless, even certain regions in developed countries are not spared the excesses of this tragedy, as in these presumably poorer, inner urban areas, maternal mortality ratios may be high as 22.8 per 100,000 live births, with up to a third of these deaths being preventable.⁹

Closer to home, the maternal mortality rate in newly industrialised Hong Kong fell steadily from 0.45 per 1000 total births to 0.05 per 1000 total births over a 25-year period between 1961 and 1985 (most deaths being due to antenatal haemorrhage, pre-eclampsia and ectopic pregnancy); this trend being accompanied by a parallel decrease in perinatal mortality as well.¹⁰ In Singapore, published official maternal mortality rates (MMR) during the same period hovered between 0.0 and 0.5 per 1000 live births and still births.¹¹ This is in stark contrast to a calculated rate of 22.9 per 100,000 deliveries, encompassing both direct and indirect maternal deaths which occurred in a major tertiary hospital in Singapore, during a 7-year period from 1986 to 1992.¹² During that time up to 1999, the official rate ranged from 0.0 to 0.1 per 1000 live births and still births. It would seem that the use of different denominators (which should not differ too markedly from each other, numerically) in these various studies would not be sufficient to account for this apparent discrepancy.

Accordingly, the present study was undertaken with the two-fold objective of estimating local, necropsy-based, MMR in an attempt to explore apparent trends in maternal deaths, as well as the nature of the discrepancy between perceived frequency of maternal deaths and the published maternal mortality statistics in Singapore. It also represents an initiative by the Centre for Forensic Medicine (CFM) to establish a database of maternal deaths reported to the coroner; this being facilitated by the fact that the CFM undertakes all coronial casework nationally.

Materials and Methods

A search was made of the autopsy records of the CFM (previously known as the Department of Forensic Medicine) in order to identify cases of maternal deaths reported to the coroner from 1990 to 1999. For the purpose of this study and in accordance with international convention, a maternal death was defined as the death of a woman while pregnant, or within 42 days of termination of pregnancy from any cause related to, or aggravated by the pregnancy, or its management.¹³⁻¹⁵ Deaths from accidental or incidental causes were accounted for separately.

The annual necropsy incidence as well as the overall prevalence of these deaths were then established and the

former were further analysed in order to determine if a statistically significant trend existed during the period in question. Subsequently, the necropsy-based, annual MMR (per 10,000 live births and still births) were estimated with the aid of the relevant data (live births and still births) published by the Registry of Births and Deaths (RBD).¹¹ The estimated MMR (both annual and composite) were compared with corresponding indices calculated from the published raw data (cases of maternal death identified by the RBD, live births and still births). Both the estimated and calculated MMR were then subjected to analysis for a linear trend.

The relevant autopsy records were examined in conjunction with the clinical and circumstantial information available and copied at the time of the respective autopsies. Where possible, the obstetric and other relevant medical records pertaining to some of the earlier cases were reviewed in order to obtain the additional data required. The objectives of this exercise in clinico-pathological correlation were to (a) determine the frequency of the various causes of maternal mortality and, thereby, identify the most common causes of maternal death; (b) determine the maternal age and racial distribution of the subjects; (c) document the range of the gestational age and parity, where known, at the time of death; and (d) classify these deaths as being direct, indirect, or fortuitous, in accordance with accepted international practice:¹³⁻¹⁵

Direct: Deaths resulting from obstetric complications of pregnancy, labour and puerperium; from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above.

Indirect: Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiological effects of pregnancy.

Fortuitous: Deaths from unrelated causes which happen to occur in pregnancy or the puerperium.

Significant sub-groups were identified and, where appropriate, subjected to comparative analysis. Major discrepancies between the principal clinical and pathological diagnoses were also noted.

Statistical analysis was performed with the aid of Epi Info 2000. Where appropriate, the χ^2 test (with Yates correction) was used to assess apparent differences in proportions between sub-groups; this being substituted with the Fisher's exact test when the expected cell value was less than 5. The significance of apparent trends in the annual necropsy incidence of maternal deaths and both the estimated and calculated MMR was determined with the application of the χ^2 test for a linear trend. Also, differences between means were analysed with the Student's *t*-test. A

P value of less than 0.05 was considered to be statistically significant.

Results

General Trends in Maternal Mortality

During the 10-year period, coroner's autopsies were conducted on a total of 51 cases of maternal deaths. This corresponded to a necropsy prevalence of approximately 0.24%, with a variable annual incidence ranging from

TABLE I: ANNUAL DISTRIBUTION OF MATERNAL DEATHS REPORTED TO THE CORONER (1990 TO 1999)

Year	Cases reported	Coroner's autopsies	% coroner's autopsies	All coroner's cases	% all coroner's cases
1990	4	2222	0.18	3332	0.12
1991	4	2188	0.18	3129	0.13
1992	6	2386	0.25	3245	0.18
1993	3	2053	0.15	3221	0.09
1994	5	2029	0.25	3306	0.15
1995	2	2028	0.10	3205	0.06
1996	3	2026	0.15	3198	0.09
1997	9	2020	0.45	3243	0.28
1998	8	2013	0.40	3346	0.24
1999	7*	1889	0.37	3121	0.22
Total/ Mean	51	20,854	0.24	32,346	0.16

χ^2 for linear trend (coroner's autopsies) = 3.985 (P = 0.046)

* Includes a case of fortuitous death from a road traffic accident

0.10% to 0.45% (Table I). Although only a small number of maternal deaths were reported to the coroner each year, it was possible to demonstrate a statistically significant upward trend in the necropsy incidence of maternal mortality from 1990 to 1999 (P = 0.046). This observation is largely explained by the concentration of nearly half (24/51) of these deaths in the last triennium (1997 to 1999).

A parallel trend was reflected in the gross estimated MMR, which ranged from 0.4 to 1.8 per 10,000 live births and still births, with a prevalence of 1.1 (95% confidence interval: 0.8 to 1.4) per 10,000 live births and still births during this time. The prevalence of direct and indirect deaths per se (with the exclusion of a solitary fortuitous death) was minimally lower at 1.0 (0.7 to 1.3) per 10,000 live births and still births (Table II). It is evident that, on average, almost twice as many maternal deaths were reported to the coroner as were officially classified as such in the published data. Accordingly, the annual and mean (prevalent) MMR calculated from published maternal mortality data were considerably lower than the corresponding necropsy-based estimates. Consequently, while a statistically significant trend was demonstrated in respect of the estimated MMR (P = 0.048), this was not replicated for the calculated MMR.

Maternal Age and Racial Distribution

The majority of subjects were Chinese (31; 60.8%), who accounted for almost two-thirds of the sample, while over

TABLE II: ESTIMATED MATERNAL MORTALITY RATES (MMR) BASED ON CASES REPORTED TO THE CORONER COMPARED WITH MMR CALCULATED FROM DEATHS CLASSIFIED AS CASES OF MATERNAL MORTALITY BY THE REGISTRY OF BIRTHS AND DEATHS (1990 TO 1999)

Year	Cases reported ¹	Cases classified ²	Live births ³	Still births ³	Estimated MMR ⁴	Calculated MMR ⁴
1990	4	1	51,142	206	0.8	0.2
1991	4	2	49,114	198	0.8	0.4
1992	6	2	49,402	171	1.2	0.4
1993	3	4	50,225	168	0.6	0.8
1994	5	3	49,554	167	1.0	0.6
1995	2	2	48,635	140	0.4	0.4
1996	3	2	48,577	150	0.6	0.4
1997	9	2	47,333	139	1.9	0.4
1998	8	6	43,664	133	1.8	1.4
1999 ⁵	7 (6)	4	43,336	125	1.6(1.4)	0.9
Total/ <i>Mean</i> ⁵	51 (50)	28	480,982	1597	1.1(1.0) ⁶	0.6 ⁷

χ^2 for linear trend:

Estimated MMR = 3.906 (P = 0.048)

Calculated MMR = 3.374 (P = 0.066)

¹ Maternal deaths reported to the coroner and subjected to autopsy

² Deaths classified as cases of maternal mortality by the Registry of Births and Deaths

³ Figures obtained from the Registry of Births and Deaths

⁴ Maternal mortality rate per 10,000 live births and still births

⁵ Figures in parentheses refer to direct and indirect deaths only (i.e. excluding the solitary fortuitous death)

⁶ 95% confidence intervals [95% CI]: 0.8 - 1.4 (0.7 - 1.3) per 10,000 live births and still births

⁷ 95% CI: 0.4 - 0.8 per 10,000 live births and still births

a quarter were Malays (14; 27.5%); the latter included an Indonesian. The remaining subjects consisted of 5 Indians (9.8%) and a Caucasian (2.0%). Their ages ranged from 19 to 41 years, with most being in the earlier half of the fourth decade of life at time of death (mean, 33.0 ± 3.7 years; median, 34.0 years).

Gestational Age and Parity

The relevant obstetric and other relevant medical records pertaining to a number of earlier maternal deaths were incomplete or unavailable at the time of the post-mortem examination, and could not be retrieved for the purpose of this study. Also, at least 5 deaths occurred at home, while 2 other women died in emergency medical departments (after they were discharged from hospitals with maternity services). Thus, the gestational age and parity of some 20% of the sample could not be determined with accuracy. The difficulty in estimating the gestational age, in the absence of complete obstetric records, was compounded by the fact that the majority of pregnancies in these cases resulted in live births (with variable postpartum infant survival), while in the remaining cases, the bodies of the fetuses or neonates were not available for autopsy.

Amongst those for whom these parameters were available (Table III), it was found that death had generally occurred during the third trimester of pregnancy, with well over half (25/43) being full-term pregnancies; only 2 deaths occurred during the first and early second trimesters each. It appears that the majority of subjects were multiparous, with two-thirds (28/40) and almost half (18/40) being gravida ≥ 2 and ≥ 3 , respectively, while a quarter (11/40) were primigravidae.

Causes of Death

The most common causes of death identified by the current study were amniotic fluid embolism (AFE) (16/51; 0.33 per 10,000 live births and still births), followed by pulmonary thromboembolism (PTE) (10/51; 0.21 per 10,000 live births and still births); both being direct maternal deaths (Table IV). Together, they accounted for just over half (51.0%) of the all maternal deaths and the majority of direct deaths over the past decade.

While the occurrence of fatal AFE was distributed fairly

TABLE III: GESTATIONAL AGE AND PARITY (WHERE KNOWN) (1990 TO 1999)

Statistic	Gestational age (weeks) n = 43	Gravida n = 40	Para n = 40
Range	8.0 to 40.0	1 to 6	0 to 5
Mean	33.7	2.8	1.6
Standard deviation	± 5.1	± 1.6	± 1.4
Median	38.0	2.0	2.0

evenly through this period, most of the cases of fatal PTE were apparently clustered in the first half of the previous decade. Thus, it was observed that from 1990 to 1994, the composite maternal mortality rate attributable to AFE was 0.3 (7/25,0347) per 10,000 live births and still births, while that for the next 5 years (1995 to 1999) was 0.4 (9/23,2232) per 10,000 live births and still births; there being no demonstrable trend in its annual incidence. In contrast, the corresponding rates for PTE were 0.3 (7/25,0347) and 0.1 (3/23,2232) per 10,000 live births and still births, respectively. Although the latter difference was not shown to be statistically significant ($P = 0.204$), possibly due to the small sub-sample size, it is still noteworthy, given the increasing overall necropsy incidence of this potentially preventable condition during the same period.

It was noted that during this time, 242 coronial autopsies were conducted on cases of fatal pulmonary thromboembolism, with a variable annual necropsy incidence ranging from 0.78% to 1.56% (Fig. 1). Accordingly, 4.1% of fatal cases of PTE were associated with pregnancy. Indeed, a significant upward trend ($\chi^2 = 5.471$; $P = 0.019$) was demonstrated during the earlier half of the last decade (1990 to 1995), with the necropsy incidence having peaked at 1.56% over 2 consecutive years (1995 and 1996). Concurrently, the number of cases during the period 1990 to 1994 was comparable to that during the period 1995 to 1999 [115 (1.06%) versus 127 (1.27%); $P = 0.164$]. Thus, it would appear that the annual incidence of maternal deaths from PTE reflected the overall trend in the incidence, rather than the absolute numerical distribution of this condition as a whole (7/115 versus 3/127; $P = 0.129$). Only 3 of these were antenatal deaths, occurring at 4, 14 and 29 weeks' amenorrhoea, respectively, while the remaining 7 occurred at postpartum intervals ranging from 1 day to 4 weeks.

Further comparative analysis showed that the subjects whose deaths were due to AFE were generally older than

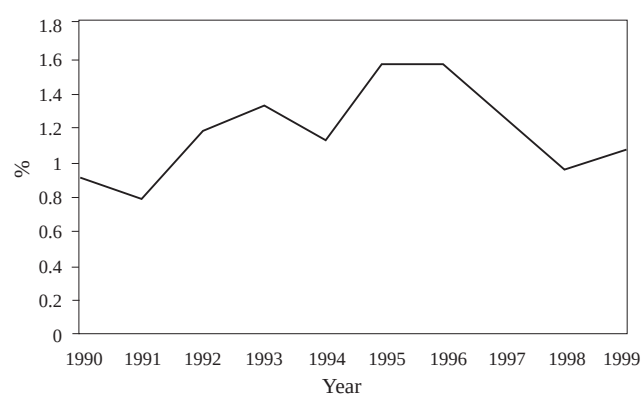


Fig. 1. Annual necropsy incidence of fatal pulmonary thromboembolism (1990 to 1999).

TABLE IV: CAUSES OF MATERNAL DEATH DETERMINED BY AUTOPSY (1990 TO 1999)

Cause of death (principal clinico-pathological diagnosis)	No. of cases (%)	Rate ¹
Amniotic fluid embolism	16 (31.4)	0.33
Massive pulmonary thromboembolism	10 (19.6)	0.21
Pulmonary disorders	6 (11.8)	0.12
Interstitial pneumonitis (consistent with viral aetiology)	3	
Bronchiectasis (severe haemoptysis)	1	
Bronchogenic adenocarcinoma	1	
Bronchial asthma	1	
Cardiovascular disorders	6 (11.8)	0.12
Acute myocarditis (consistent with viral aetiology)	2	
Severe IHD/AMI	2	
Infective endocarditis (acute MR)	1	
Mitral stenosis (LVF and cerebral thromboembolism)	1	
Cardiovascular with secondary pulmonary involvement	1 (2.0)	0.02
Infective endocarditis with massive pulmonary vegetation embolism ²	1	
Postpartum haemorrhage	3 (5.9)	0.06
Utero-vaginal rupture (traumatic forceps-assisted delivery)	2	
Placenta praevia	1	
Ectopic pregnancy	2 (3.9)	0.04
Cerebrovascular disorders	1 (2.0)	0.02
Spontaneous acute intracerebral haemorrhage ³	1	
Pregnancy induced hypertension	1 (2.0)	0.02
Eclampsia (severe cerebral haemorrhage)	1	
Molar pregnancy	1 (2.0)	0.02
Multiple injuries	3 (5.9)	0.06
Fall from a height (suicidal)	2	
Road traffic accident	1	
Hanging (suicidal)	1 (2.0)	0.02

AMI: acute myocardial infarction; IHD: ischaemic heart disease; LVF: left ventricular failure; MR: mitral regurgitation

¹ Per 10,000 live births and still births

² A case of apparent incomplete abortion overseas followed by, approximately a month later, evacuation of retained products of conception by dilatation and curettage locally. Post-mortem culture of the vegetation arising from the tricuspid valve yielded Group B *Streptococcus*. However, as the valve itself was defective (myxoid degeneration) and could have predisposed to infective endocarditis per se, it was not possible to classify this case as one of fatal septic abortion conclusively.

³ Clinical diagnosis of subarachnoid haemorrhage from a ruptured berry aneurysm; none was found at autopsy.

their counterparts who died from other causes [mean, 35.1 versus 32.2 (95% confidence interval for difference, 0.4 to 5.8) years; $P = 0.006$] and even more so when compared specifically to those who died from fatal PTE [35.1 versus 29.8 (2.9 to 7.7) years; $P < 0.001$].

In addition, it was also observed that cases of AFE were apparently associated with multiparity to a greater extent than the sample as a whole, as well as other causes of death [mean gravida, 3.5 (SD, ± 1.6) versus 2.8 (± 1.6) versus 2.4 (± 1.6)], with only 2 subjects being primigravidae. However, incomplete data on parity (particularly in relation to PTE, where complete information was available in only 6 out of 10 cases) precluded a more precise analysis of these observed differences.

No notable differences in age, gestational age, or parity were found amongst the other direct or indirect causes of death.

There were at least 13 peri-procedural deaths (including 1 intraoperative death), of which 3 were due to massive PTE and another 3 from postpartum haemorrhage (unrelated to AFE). The remaining 7 cases were due to AFE (4) and ischaemic heart disease (1), acute viral myocarditis (1) and viral interstitial pneumonitis (1), respectively (Table V).

Significantly, at least 4 deaths were overtly iatrogenic in nature. Two of these resulted in fatal postpartum haemorrhage due to utero-cervical (case 37) and vaginal (case 38) rupture, associated with forceps-assisted delivery; the former was complicated by septicaemia, disseminated

TABLE V: PERI-PROCEDURAL MATERNAL DEATHS REPORTED TO THE CORONER (1990 TO 1999)

Case no.	Age (years)	Gestation (weeks)	Clinical presentation/diagnosis	Procedure(s)	Autopsy findings
20	32	36	Previous termination of pregnancy; current pregnancy: diminished foetal movement, PPH.	SI (ARM); sub-total hysterectomy & right salpingo-oophorectomy	PM histology: foetal squames and thromboemboli in pulmonary microvasculature, consistent with AFE.
22	34	8	Uterine fibroids; collapsed shortly after pelvic ultrasonography; massive PTE suspected; protracted and vigorous resuscitation instituted.	Laparotomy and repair of liver lacerations.	Massive saddle PTE; 7 sutured, liver lacerations, 1 stellate (probably resuscitative injuries); haemoperitoneum (1 l); bilateral haemothoraces (0.75 l); uterine fibroids; IUD (foetus <i>in situ</i>)
23	29	36	Abruption placenta, IUD, PPH, DIC, transient pre-eclampsia	Sub-total hysterectomy	PM histology: keratinous squames and fibrin-platelet emboli in pulmonary microvasculature, consistent with AFE.
25	36	17	Pregnancy-induced hypertension, with past history of gestational diabetes mellitus and a previous still birth.	Prostaglandin-induced abortion	IHD: mildly enlarged heart (380 g) with concentric hypertrophy; severe coronary atherosclerosis, with pin-point stenosis of LAD, associated with intimal plaque haemorrhage.
28	34	38	Placenta praevia (grade 3), with PPH haemorrhage; ?AFE.	Emergency LSCS, postpartum tubal ligation; total hysterectomy.	Severe cerebral oedema (uterus not available for examination); no vaginal lacerations; PM histology: moderate interstitial lymphocytic infiltrates in heart and lungs; no foetal squames in pulmonary microvasculature (no evidence of AFE).
33	26	40	Recent history of postpartum DVT (1 month), apparently received anticoagulant therapy; however, developed massive PTE, followed by MOF; protracted and vigorous resuscitation at time of initial collapse; died intraoperatively.	Emergency pulmonary embolectomy (removal of 20 g thromboembolus); laparotomy and repair of liver lacerations.	Organising, peripheral thromboembolus in right upper lobar pulmonary artery; pulmonary haemorrhage; contused left hemi-diaphragm; haemoperitoneum (1l); multiple liver lacerations (probably resuscitative injuries).
34	34	14	Bilateral ovarian endometriotic cysts; collapsed suddenly on 1 st POD; clinical suspicion of PTE.	Antenatal elective laparotomy and bilateral cystectomy.	Laminated pulmonary thromboemboli occluding both right and left pulmonary arteries; pulmonary infarcts in upper and lower lobes of right lung; IUD (foetus <i>in situ</i>).
36	32	38	Cephalopelvic disproportion	Emergency LSCS	PM histology: interstitial pneumonitis, consistent with a viral aetiology.
37	38	38	PPH: cervical laceration/uterine rupture; lacerated pelvic veins; subsequently, developed septicaemia, DIC, MOF; past history of oligohydramnios.	Forceps-assisted delivery for poor maternal effort; sub-total hysterectomy and repair of iliac veins.	Bronchopneumonia, septicaemia, moderate cerebral oedema, severe retroperitoneal haemorrhage; extensive omental and mesenteric haemorrhage; diffuse alveolar damage (histology); uterus not available for examination; vaginal intact.
38	39	35	Advanced maternal age; IVF, twin pregnancy; severe pre-eclampsia; PPH.	Induction of labour for impending eclampsia; forceps-assisted delivery; repair of vaginal lacerations.	Multiple lacerations and perforation of right lateral vaginal wall (evidence of surgical repair); cervix effaced (no utero-cervical laceration) diffuse, haemorrhagic endometrial infarction; PM histology: platelet-fibrin thrombi, focal inflammatory infiltrates in myocardium.

TABLE V: Contd.

Case no.	Age (years)	Gestation (weeks)	Clinical presentation/diagnosis	Procedure(s)	Autopsy findings
45	39	40	Pregnancy-induced hypertension/eclampsia; collapsed during 1 st stage of labour (induced); PPH, DIC, renal impairment, HIE culminating in brain death.	Prostin induction; forceps-assisted delivery (live infant).	Early liquefaction of brain consistent with brain death; IHD: LAD-50%, LCx-25% stenoses; no utero-cervical or vaginal injury; PM histology showed evidence of AFE: squames, mucin, fibrin emboli in pulmonary microvasculature.
48	29	38	Past history of LSCS (twice); recent antenatal episode of chickenpox; 2 hours after apparently uneventful 3 rd (elective) LSCS, developed convulsions and collapsed followed by uterine atony, PPH, DIC; ?AFE	Elective LSCS; emergency sub-total hysterectomy	Bilateral pleural effusions (right: 300 mL, left: 450 mL) and ascites (650 mL) (blood-stained fluid); myocardium appeared mottled; PM histology: features consistent with acute myocarditis.
49	40	38	Foetal distress (moderate to severe meconium staining); ?AFE	ARM; emergency LSCS	PM histology: squames and mucin emboli in pulmonary arterioles and alveolar capillaries

AFE: amniotic fluid embolism; ARM: artificial rupture of membranes; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; HIE: hypoxic-ischaemic encephalopathy; IHD: ischaemic heart disease; IUD: intra-uterine death; IVF: in vitro fertilisation; LAD: anterior descending branch of left coronary artery; LCx: circumflex branch of left coronary artery; LSCS: lower segment caesarean section; MOF: multi-organ failure; PM: post-mortem; POD: postoperative day; PPH: postpartum haemorrhage; PTE: pulmonary thromboembolism; SI: surgical induction

intravascular coagulation (DIC) and multi-organ failure, and the latter by pre-eclampsia. The other 2 cases (22 and 33) were of massive PTE complicated by haemoperitoneum from liver lacerations, deemed to be consistent with resuscitative injuries. In both of the latter cases, the subjects underwent laparotomy and surgical repair of the liver lacerations while pulmonary embolectomy was also performed on one of them (case 33).

During this time, there were 3 cases of suicide: 2 deaths were due multiple injuries sustained from falls from heights, that occurred in the third trimester (at 28 and 37 weeks' gestation, respectively), while the remaining case was one of hanging at approximately 12 weeks' gestation (as estimated at autopsy). All 3 cases were associated with the intra-uterine death of the foetuses, which were apparently normal. The presumptive, psychiatric indirect death rate was therefore approximately 0.06 per 10,000 live births and still births.

Classification of Maternal Deaths

Over two-thirds (33/51; 0.68 per 10,000 live births and still births) of the cases were direct maternal deaths, while most of the remainder (17/51; 0.35 per 10,000 live births and still births) were indirect deaths. The former comprised AFE, PTE, postpartum haemorrhage, ectopic pregnancy, eclampsia and molar pregnancy; while the latter consisted primarily of pre-existing cardiovascular, pulmonary and cerebro-vascular disorders which were, presumably, aggravated by the physiological effects of pregnancy as well as instances of suicide. There was only 1 fortuitous

death from a road accident, involving the pillion of a motorcycle.

Major Diagnostic Discrepancies

When compared against the autopsy findings, it appeared that only a little more than half (20/33) of the cases of direct maternal death had a correct clinical diagnosis of the probable cause of death. Similarly, the clinical diagnostic accuracy in cases of indirect deaths was only marginally higher (9/16, excluding the single case of suicidal hanging).

Specifically, the proportions of clinical diagnoses corroborated by post-mortem examination in the major diagnostic categories of direct and indirect maternal deaths were as follows: AFE: 7/16; massive PTE: 6/10; cardiovascular and pulmonary disorders: 6/13; postpartum haemorrhage: 3/3; ectopic pregnancy: 2/2, cerebrovascular disorders: 1/1; pregnancy-induced hypertension: 1/1; molar pregnancy: 1/1 and multiple injuries: 3/3.

Discussion

The results of this study indicate that there was a statistically significant, upward trend in maternal deaths, both in terms of the coronial necropsy incidence as well as the estimated (necropsy-based) MMR during the last decade. There appeared to have been a predilection for multiparous women in their fourth decade of life and the third trimester of pregnancy or during the peripartum period. This was accompanied by a disproportionately high incidence amongst Malay women, who accounted for more than a quarter of the entire sample.

However, it is unclear if this general trend actually represents a progressive upswing in the frequency of maternal mortality, or whether it merely reflects more conscientious reporting of these deaths to the coroner (a phenomenon alluded to in earlier publications on perioperative deaths in Singapore^{16,17}), possibly arising from a heightened awareness of the medico-legal implications of maternal deaths, particularly during the last triennium of the period in question.

Certainly, given what is perceived to be an increasingly hostile medico-legal climate in which medical practitioners are required to work, almost every maternal death should be regarded as a cause for concern and be made the subject of a thorough audit or inquiry, both at the departmental and institutional level. As this study demonstrates, a maternal death in Singapore, perhaps best epitomised by AFE (which appears to be the most frequent cause of maternal mortality locally), tends to present as a case of sudden and unexpected peripartum death, often (although not invariably) in apparently healthy women with an uncomplicated antenatal history. Also, an autopsy, supplemented by post-mortem histopathology, would be required to establish or confirm the clinical diagnosis. Moreover, there exists the ever-present threat of medical litigation or, at least, that of allegations of sub-standard obstetric care being made against the medical and nursing staff in attendance.^{18,19} Thus, it would hardly be surprising that these considerations have, over the years, prompted obstetricians to be more vigilant in reporting such deaths to the coroner.

Furthermore, it was observed that the estimated MMR, which was derived from a combination of coronial and published demographic data, far exceeded the published and calculated MMR. Part of the reason could be the fact that, at least until 1999, the published crude MMR were given as the number of deaths per 1000 live births and still births, correct to one decimal point;¹¹ a practice which might have engendered the impression that maternal deaths are rare occurrences or almost non-existent locally, as the official rates of 0.0 to 0.1 per 1000 live births and still births (from 1980 to 1999) might suggest. Accordingly, when the rates were calculated using the published demographic data, but raised upon a denominator of 10,000 live births and still births, more realistic figures emerged (Table II). It is understood that, presently, the latter denominator is being employed in the official reporting of the local MMR, this having taken effect since the year 2000.

Another possibility could be that the published MMR might largely be based on direct maternal deaths, as the official definition of maternal mortality is “the deaths of mothers owing to deliveries and complications arising from pregnancy, childbirth and puerperium”, without explicit reference to direct, indirect or fortuitous deaths.¹¹

If this were indeed the case, then it would be perfectly understandable as the certified causes of indirect maternal mortality may not reflect the true nature of these deaths (since information regarding pregnancy is not explicitly sought after in the existing death registration procedure). However, even this would not account for the difference between the total number of direct maternal deaths reported to the coroner and that of all maternal deaths reflected in the published demographic data (33 versus 28; Table II).

On the strength of the available evidence, it would appear that the estimated, annual MMR, as well as the prevalence of maternal mortality, over the last decade, compare favourably with those of developed nations, such as the United Kingdom, where rates of 10.1, 9.9 and 12.2 direct and indirect deaths per 100,000 maternities were reported over three consecutive triennia encompassing the periods 1988 to 1990, 1991 to 1993 and 1994 to 1996, respectively¹³ (these being equivalent to rates of approximately 1.0, 1.0 and 1.2 per 10,000 maternities, respectively); as well as to much of the rest of middle and northern Europe⁸ and the United States.^{7,9}

However, this provisional assessment is subject to the caveat that it holds true only if it may be assumed that most, if not all, maternal deaths were referred to the coroner. During the period in question and at the time of writing, it was not mandatory to report all maternal deaths and, consequently, obstetricians could exercise considerable discretion in this matter. Hence, it is entirely possible that such deaths may well have been under-reported, at least until the earlier part of the last decade. Thus, it would not be possible to determine, with any certainty, the extent to which the actual and published MMR deviated from the true MMR over the years.

In the light of these considerations, it is imperative that a comprehensive database of maternal deaths, that is updated continually and contemporaneously, is established and maintained. This is because reliance on death registration alone, clearly, is inadequate for the purpose of monitoring trends in maternal mortality. Moreover, death certificates do not provide critical obstetric information, such as gestational age and parity, which, as this study demonstrates, may be irretrievable retrospectively. Also, the frequency of major clinico-pathological diagnostic discrepancies disclosed by this study seems to reinforce the need for a thorough post-mortem examination in every case of maternal death.^{20,21}

With respect to the specific causes of maternal mortality, it appears that AFE was the most frequent cause, accounting for nearly a third of all maternal deaths locally, followed by PTE which was substantive cause of death in a fifth of cases. Their estimated prevalence rates of 0.33 and 0.21 per 10,000 live births and still births, respectively, apparently

exceeded, or were comparable to, the corresponding rates reported in the United Kingdom, over 3 successive triennia from 1988 to 1996 (AFE: 4.3-7.7 per million maternities, being equivalent to 0.04-0.08 per 10,000 maternities; PTE: 14.0-21.8 per million maternities, or approximately 0.14-0.22 per 10,000 maternities).¹³

Accordingly, it would appear that the local prevalence of fatal AFE was at least 4 times higher than that in the United Kingdom, over a comparable period of time.

Concurrently, a high index of clinical suspicion for venous thrombosis and PTE is clearly warranted, as the latter can no longer be dismissed as being rare or uncommon in Singapore.²² It is submitted that the somewhat different denominators used in both instances cannot possibly account for the very considerable variance in the frequencies observed. Moreover, if maternal deaths have in fact been under-reported locally, then the actual rates of both conditions could very well be higher than those reflected in this study. By the same token, although the comparative rates for pregnancy-induced hypertension, postpartum haemorrhage, ectopic pregnancy, cardiovascular and other indirect causes appeared to be relatively low, one cannot be certain if these estimates are in fact representative of the actual situation at hand. In any event, further examination of the relatively high rate of AFE in Singapore is indicated.

The finding that the women who died from AFE were, on average, 3 to 5 years older than those who died from other causes of death (particularly PTE) and also displayed a higher degree of multiparity, accords with similar observations made in earlier publications,^{18,19,23,24} although it may occasionally afflict young, primigravidae as well.²⁵ It is generally considered to be a rare peripartum complication, with an incidence which is thought to vary widely between 1:8000 and 1:80,000 deliveries, with a high mortality rate of 80% to 90%.²⁶⁻²⁸ The rate of 0.33 per 10,000 live births and still births, which corresponds to a frequency of approximately 1:30,000 deliveries, in the present series, seems to be consistent with these estimates. The intriguing and somewhat enigmatic pathophysiology of AFE (a summary of which is provided in the appendix) more than hints at the diagnostic, therapeutic and medico-legal difficulties that it presents. At the very least, the complexity of the subject renders the inevitable task of explaining how an apparently healthy, if older, multiparous patient, with a largely uneventful pregnancy could have died so suddenly, unexpectedly and dramatically in the course of childbirth, to the bereaved family of such a patient, most difficult and daunting, indeed. The spectre or threat of medical litigation tends to loom rather large in a situation such as this, at least initially and, quite possibly, well after the event.

The diagnostic challenge imposed by AFE have in fact

spawned numerous serological and immunological studies on this subject. Some of these have led to the development of non-invasive and purportedly sensitive diagnostic methods employing the monoclonal antibody TKH-2, which is directed at the sialyl Tn structure (NeuAc α 2-6GalNAc α 1-Ser/Thr epitope), or STN, a glycoprotein contained in amniotic fluid and meconium. These have demonstrated much higher serum levels of STN in patients with AFE and AFE-like symptoms than those with clear, or even meconium-stained, amniotic fluid, unassociated with AFE.^{29,30} Immunohistochemical demonstration of sialyl Tn with TKH-2 has also been successfully demonstrated in the pulmonary vasculature in patients with AFE.^{30,31} Intense expression of endothelin-1, a potent vasoconstrictor and bronchoconstrictor, has also been demonstrated in amniotic squames, with weaker staining of the alveolar and bronchiolar epithelium, as well as the alveolar macrophages and vascular endothelium of patients in AFE.³²

In the author's experience, the routine use of the Attwood's stain (a combination of phloxine tartrazine for microemboli of keratin squames, and Alcian green for mucin) as well as appropriate fat stains for vernix caseosa would generally suffice. Occasionally, however, foetal squames may be difficult to detect in histological specimens of the lungs and other organs, whereupon a panel immunohistochemical stains for keratin (such as CK 7, CK 20, AE 1/3 and Cam 5.2) may be employed to good effect. It must be emphasised that, ultimately, a thorough clinico-pathological correlation and the systematic exclusion of other causes of maternal death, form the basis of a definitive diagnosis of AFE.^{18,19}

The incidence of fatal PTE associated with pregnancy seemed to vary in tandem with the overall necropsy incidence of this potentially preventable and treatable complication. Despite being apparently the second most common cause of maternal death over the last decade, it was suspected or provisionally diagnosed in only a little over half of the women who died from this condition. This seems to be consistent with the results of an earlier retrospective study, in which pregnancy and surgery were predisposing factors in 4.3% and 41.4%, respectively, of deaths from PTE that were reported to the coroner. That study, covering 5-year period from 1989 to 1993, demonstrated a generally low clinical index of suspicion for this condition, which was unsuspected in 77.1% of subjects who died whilst under medical care.²² The results of the present study seem to suggest that clinical diagnostic accuracy had not improved thereafter, at least with respect to fatal PTE occurring in obstetric practice.

It is not known if any of these women had hereditary thrombophilia, such as the antiphospholipid antibody syndrome, lupus anticoagulant, deficiencies of antithrombin, proteins C and S, factor V Leiden,

prothrombin genetic mutations (F2G20210A), a genetically transmitted excess of histidine-rich glycoprotein (HRG) which inhibits plasminogen and heparin.^{22,33-39} Almost none of the women in this series was particularly obese, nor was there a history of previous or recurrent venous thromboembolism.

Notably, a recent Japanese study⁴⁰ involving 16 pregnant women aged 29 to 39 years showed that 4 of 12 subjects who developed antenatal deep vein thrombosis (DVT) without PTE had severe thrombophilia (antiphospholipid antibody syndrome and antithrombin deficiency) or a history of venous thrombosis, while the remaining 8 patients in this sub-group developed DVT after undergoing caesarean section. Of the 4 patients who developed postoperative PTE, 3 also underwent caesarean section, with the fourth being subjected to ovarian cystectomy at 13 weeks' gestation; the latter bearing an uncanny resemblance to case 34 (Table V) in the present series, wherein 3 of the 10 deaths from PTE occurred perioperatively. The authors suggest that appropriate preventive measures, such as prophylactic anticoagulant therapy, might be administered selectively to obstetric patients at risk for DVT/PTE, in a situation where the incidence of venous thrombosis is generally low. In this respect, it should be noted that the local prevalence of fatal PTE in general, and in obstetric practice in particular, can no longer be dismissed as being insignificant.

On the other hand, it has also been demonstrated that the risk of recurrent antepartum DVT in women with a history of venous thromboembolism (associated with a temporary risk factor) but without thrombophilia is negligible, as compared with those with thrombophilia (2.4%) or a combination of thrombophilia and previous venous thromboembolism (5.9%). This would seem to suggest that antepartum prophylaxis with heparin is not necessarily warranted, even in patients with a previous episode of venous thromboembolism, unless thrombophilia is present.⁴¹ However, the controversy is further complicated by recent evidence of superficial vein thrombosis being an independent risk factor for DVT and the consequential argument that prophylaxis is warranted for pregnant women with this condition.⁴²

The ongoing debate extends, with equal intensity, to the choice of anticoagulant therapy for DVT. It has been observed that warfarin may cross the placental barrier and thus result in foetal complications or intrauterine death, whereas heparin, which does not pass through the placenta, may not be amenable to long-term use and predispose to osteoporosis and neurologic complications.⁴³ Recently, evidence has emerged that warfarin embryopathy occurs only when oral anticoagulants are administered between the 6th and 12th weeks of gestation and might not be

teratogenic when used in the first 6 weeks of gestation.⁴⁴ Nevertheless, it is said that low molecular weight heparin is still largely the anticoagulant of choice during pregnancy, on account of its apparent absence of teratogenicity and its improved efficacy and safety over unfractionated heparin.⁴⁵⁻⁴⁷ In any event, given the inherent complications of anticoagulation, not least of which is major haemorrhage, it is clear that effective thromboprophylaxis (and thrombolysis) must be tailored to the individual patient.⁴⁸ Alternatively, inferior vena cava filters may be inserted in patients who develop PTE or significant bleeding while on anticoagulation, as well as those with heparin-induced thrombocytopenia.⁴³

In any event, authoritative guidelines for prophylactic and therapeutic anticoagulation (as well as the management of the attendant complications) abound, even if most of these do not specifically or exclusively address the issue of the optimal management of maternal venous thromboembolism.⁴⁹⁻⁵³ Given the fact that PTE is potentially preventable and can no longer be considered a rare occurrence during pregnancy or the puerperium, failure to diagnose it, or at least, to maintain a reasonably high clinical vigilance for it, may result in serious medico-legal consequences.²² Conversely, the very real risk of major haemorrhage, as well as the various other complications associated with prophylactic anticoagulation alluded to above, would also be a valid and often perplexing cause for concern amongst obstetricians as well as other clinicians faced with the spectre of DVT/PTE. Accordingly, there may well be a need for national evidenced-based or, at least, consensus-derived guidelines for safe and effective anticoagulation in obstetrical and, for that matter, other areas of clinical practice. One might argue that there is a certain urgency in this matter as increasingly clinicians seem to be required to perform a difficult balancing act (fatal PTE versus fatal major haemorrhage) whilst managing patients with multiple and complex co-morbidity, as the daily forensic reviews of such deaths as are reported to the coroner would suggest.

The remaining 9 cases of direct maternal deaths comprised postpartum haemorrhage, ectopic pregnancy, eclampsia and molar pregnancy, at estimated rates of 0.06, 0.04, 0.02 and 0.02 per 10,000 live births and still births, respectively. The frequencies of these conditions compare favourably with the latest available statistics obtained from the United Kingdom at the time of writing: during the triennium of 1994 to 1996 (when there were almost 2.2 million maternities), the corresponding rates were 5.5, 5.4, 9.1 and (apparently) 0 per million maternities¹³ (or approximately 0.06, 0.05, 0.09 and 0 per 10,000 maternities), respectively. It would appear that deaths from pregnancy-induced hypertension were rare over the last decade in Singapore,

although it was the second most common cause of direct maternal death in the United Kingdom during the same triennium.¹³

Locally, there were no overt cases of fatal genital tract sepsis reported to the coroner, apart from an instance of infective endocarditis which might have been attributable to an infection arising from retained products of conception from an earlier, incomplete induced abortion, although this was unproven (Table V). There was no definite record of death from toxic shock syndrome, even though this was suggested retrospectively by an obstetrician serving as an independent clinical expert in a coroner's inquiry into a maternal death, which was attributed to cardiovascular causes. In contrast, the maternal death rate from sepsis was 6.4 per million maternities in the United Kingdom during the last reported triennium.¹³ It may be noted, in passing, that together with PTE and AFE, sepsis is one of the major causes of non-obstetric shock.

Despite the fact that deaths from thrombotic microangiopathy have been reported,⁵⁴ only an equivocal case of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome was encountered in a patient who succumbed to massive thromboembolism in the present series.^{55,56} The other related syndromes comprise thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, lupus vasculitis, acute fatty liver of pregnancy and antiphospholipid antibody syndrome, which were not recorded in this study.⁵⁵⁻⁶⁸ Similarly, there were also no deaths from rare conditions such as spontaneous rupture of the spleen in pregnancy,⁶⁹⁻⁷² gestational choriocarcinoma,⁷³⁻⁷⁵ or air embolism related to drug abuse or sexual activity.⁷⁶⁻⁷⁸

In the present study, direct deaths were apparently twice as common as indirect deaths (33 versus 17). This too stands in rather stark contrast to the situation in the United Kingdom, where equal numbers of direct and indirect deaths (134 each) were reported for the period 1994 to 1996.¹³ Accordingly, the estimated total direct and indirect death rates in Singapore over the last decade were 0.68 and 0.35 per 10,000 live births and still births, respectively, while the corresponding figures in the United Kingdom over 3 consecutive triennia (1988 to 1996) ranged from 5.6 to 6.1 and 3.9 to 6.1 per 100,000 maternities, respectively.¹³ Further comparison between the two data sets shows an apparent preponderance of cardiac-related deaths (6/15) locally, whereas in the United Kingdom, cardiovascular disorders accounted for a smaller proportion of indirect deaths (39/134), although the respective rates might suggest otherwise (0.12 per 10,000 live births and still births vs 17.7 per million maternities).¹³

However, given the possibility of under-reporting locally, one cannot be certain if the disproportionately low rate of indirect deaths was a spurious one. Indeed, under-reporting

is a problem that has afflicted even the well established Confidential Enquiry into Maternal Deaths in the United Kingdom, at least until the last reported triennium when it had the benefit of an advanced computer programme (belonging to the Office of National Statistics), which enabled it to identify maternal deaths that would otherwise have been unrecognised.¹³

Of the 4 overt iatrogenic deaths, 2 were due to uterine and vaginal trauma, respectively. Both of the latter were attributable to forceps-assisted delivery and, it might be noted, received verdicts of misadventure upon inquest. It appears that in neither case was there a history of previous caesarean section, which has been said to increase the risk of maternal morbidity and mortality quite considerably.⁷⁹⁻⁸¹ While a trial of vaginal birth after a previous caesarean section has been recommended,⁸² a recent report purportedly showed that the risk of uterine rupture, among women undergoing vaginal delivery following spontaneous labour, was at least 3 times higher than those who underwent a second caesarean section without spontaneous labour.^{83,84} Sudden death following caesarean section for placenta praevia and placenta accreta has also been reported; this being attributed to DIC consequent to extensive embolisation of trophoblastic tissue.⁸⁵ Although case 28 was 1 of the deaths from postpartum haemorrhage following emergency caesarean section for placenta praevia, there was no evidence of placenta accreta or trophoblastic embolisation.

The 2 remaining cases of overt iatrogenic death involved patients who sustained severe resuscitative liver injuries following massive PTE; one of which had previously been reported.⁸⁶ Of course, it could quite justifiably be argued that the underlying PTE would have been a sufficient cause of death in the ordinary course of nature. It is, perhaps, ironical that it is precisely because both patients had been resuscitated successfully, if only transiently, that the consequent severe peritoneal haemorrhage from the liver lacerations had to be taken into account in ascertaining the cause of death.

Mention should be made of the 3 cases of maternal suicide in the present series, all of which occurred antenatally rather than during the puerperium. This would seem to be in accord with the findings of a recent study which purportedly demonstrated that symptoms of depression are not more common or severe after childbirth than during pregnancy.⁸⁷ It is not known what the predisposing factors were in these cases. Nevertheless, it is of interest to note that a Finnish study, covering the period 1987 to 1994, showed that the suicide rates associated with miscarriage and induced abortion were significantly higher than that associated with childbirth (18.1, 34.7, 5.9 per 100,000 pregnancies, respectively).⁸⁸

The presumptive psychiatric indirect death rate of 0.06 per 10,000 live births and still births seems to have exceeded the corresponding rate of 4.1 per million maternities (or approximately 0.04 per 10,000 maternities) in the United Kingdom during the 1994 to 1996 triennium, when 9 maternal suicides (excluding late indirect deaths) were recorded, comprising 5 antenatal and 4 postpartum deaths (within 6 weeks of delivery).¹³

Finally, the subject of whether short and long inter-pregnancy intervals has any bearing upon maternal morbidity and mortality appears to be rather controversial, at present.^{2,89-91} This is an issue that the present study was not designed to address and could perhaps be examined in a more comprehensive, follow-up study on maternal morbidity and mortality. Certainly, there can be little doubt that subject of maternal mortality, tragic and ridden with medico-legal implications as it is, will remain a fascinating if sobering one well into the future. In any event, an ongoing, multi-disciplinary, systematic review of all relevant clinico-pathological information relating to all maternal deaths, perhaps supported by compulsory reporting of these deaths to a central collating agency, could well serve to provide a more realistic appraisal of maternal mortality in Singapore.

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Appendix I: The Pathophysiology of Amniotic Fluid Embolism: A Conundrum

It is said that the occurrence of AFE is both unpredictable and unpreventable, while its management is largely empirical, being largely limited to the maintenance of oxygenation, circulatory support and the correction of coagulopathy.⁹² However, it is also known that sub-clinical or asymptomatic embolisation of amniotic fluid (containing foetal squames, mucin, vernix caseosa and lanugo hair), as well as trophoblastic tissue, is not uncommon.⁹³⁻⁹⁶ Accordingly, it has been postulated that it is the introduction of abnormal amniotic fluid into the maternal circulation which engenders the rapidly fatal cascade of haemodynamic disturbance and haematological derangement characteristic of AFE.⁹⁷

It is thought that the pathophysiology of AFE consists of an initial, transient, phase of intense pulmonary vasospasm. This causes in severe, acute pulmonary hypertension profound hypoxia^{97,98} and left ventricular failure (due to a combination of hypoxia and a direct depressant effect on the myocardium^{99,100}) and often presents as a combination of shock, dyspnoea, cyanosis, convulsions and sudden collapse in the peripartum period.^{18,19} These effects account for about half of these deaths within the first hour.^{18,19,97,98} Subsequently, DIC supervenes in approximately 40% of the survivors of the initial haemodynamic disturbance.⁹⁷⁻¹⁰¹ AFE-induced coagulopathy has been attributed to its thromboplastin-like properties; its ability to induce platelet aggregation and to promote the release of platelet factor III; as well as the activation of factor X and the complement cascade.¹⁰¹⁻¹⁰³ Also, the release of trophoblastic tissue (with its attendant thromboplastin-like effects) is believed to play a major role in the development of DIC.²⁸

Recently, amniotic fluid was found to contain tissue factor pathway inhibitor (TFPI), a natural inhibitor of tissue factor (TF), at a mean concentration of 38.7% of that in plasma. Conversely, the level of TF in amniotic fluid was almost 45 times higher than the plasma concentration. This observation has led to the postulation that the entry of amniotic fluid into the maternal circulation may upset the plasma TFPI-TF equilibrium, thereby triggering DIC.¹⁰⁴

An anaphylactic response to foetal antigens has long been implicated in AFE. This has been attributed to mediators of hypersensitivity, such as leucotrienes and prostaglandins¹⁰⁵ (which are present in amniotic fluid in increased concentrations during labour¹⁰⁶), as well as proteolytic enzymes such as histamine and serotonin.¹⁰⁷ An immunohistochemical study involving the morphometric quantification of pulmonary mast cell tryptase showed a marked increase in the number of these cells in subjects who died of AFE, that was similar in magnitude to that observed in cases of fatal anaphylactic shock, in comparison with controls who had succumbed to trauma.¹⁰⁸ However, a recent study evaluating the potential role of immunologic mechanisms involving mast cell degranulation and complement activation in AFE demonstrated that while maternal peripartum levels of C3 and C4 were low, serum tryptase and urinary histamine measurements yielded negative results. This led the investigators to infer that although complement activation occurs in AFE, mast cell degranulation (and therefore anaphylaxis) is not implicated in its pathophysiology.¹⁰⁹ Clearly, the current evidence for anaphylaxis in AFE is somewhat conflicting, to say the least.

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