AMNIOTIC FLUID EMBOLISM: A REVIEW OF 10 FATAL CASES

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ABSTRACT

A study of 10 fatal cases of amniotic fluid embolism, confirmed by autopsy and post-mortem histological examination, that occurred in Singapore between 1983-1992, showed that the majority (9 cases) were multiparous, with between 2-4 previous normal pregnancies each. Seven had uneventful antenatal histories. In all cases, the clinical onset was sudden and unexpected, having occurred during the first stage of labour in 8 subjects and being associated with convulsions in 5. There were seven cases of coagulopathy, with 6 of disseminated intravascular coagulation. Overall, foetal survival was poor. Three cases were associated with induction of labour, while another 3 occurred after augmentation. Emergency caesarean sections were performed in 5 cases.

Autopsy demonstrated moderate to severe pulmonary oedema in 9 cases, accompanied by pulmonary haemorrhage in 6. Mild coronary atheroma was present in 6 cases, with 3 showing subendocardial haemorrhage. Significant utero-cervical ruptures or lacerations were found in 3 cases. Microscopy demonstrated the presence of squamous epithelial emboli within the pulmonary vasculature in all cases. Other histological features included fibrin microthrombi (3 cases), alveolar and pulmonary interstitial inflammation, focal myocardial and hepatocellular necrosis, and myocardial interstitial inflammation.

Although the precise pathogenesis of amniotic fluid embolism has remained somewhat enigmatic, recent evidence points towards a combination of a severe haemodynamic disturbance followed by secondary coagulopathy in about 40% of patients who survive the initial event. Leucotrienes, prostaglandins and other vasoactive substances contained in amniotic fluid are postulated to play a fundamental role in its pathogenesis. Amniotic fluid is also thought to possess thromboplastin-like properties. As with other causes of maternal death, a thorough medico-legal autopsy is warranted.

Keywords: amniotic fluid embolism, sudden maternal death

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INTRODUCTION

Amniotic fluid embolism was first reported by Meyer in 1926[1]. It is a rare cause of sudden maternal death that may occur during labour or, less frequently, in the early post-partum period. The incidence of amniotic fluid embolism has been variously estimated to be between 1:8,000 to 1:80,000 pregnancies, it being associated with a high mortality rate of 80% or more[2-4].

Its significance, from a medico-legal perspective, resides in, firstly, its presentation as a form of sudden, unexpected peripartum death in generally healthy women who often have an uncomplicated antenatal obstetric history (but who are usually older and multiparous); secondly, the fact that the cause of death can only be conclusively ascertained at autopsy, supplemented by post-mortem histopathology; and thirdly, the very real possibility that allegations of medical negligence may be made against the medical staff in attendance. In addition, such deaths fall within the general ambit of maternal mortality which warrants a thorough investigation, both as to their causation and the adequacy of obstetric care.

The purpose of the present study is to determine the clinico-pathological aspects of amniotic fluid embolism in Singapore, observed over the past decade, in the light of the proposed theories of its aetiology and pathogenesis.

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MATERIALS AND METHOD

The case records of the Department of Forensic Medicine for the period 1983-1992 were reviewed. From a total of 33 maternal deaths reported to the Coroner, 10 cases of amniotic fluid embolism were extracted for further study. Clinico-pathological correlations were established, this being facilitated by access to copies of the clinical records that had been available at the time of the autopsy, and to the relevant Coroner's case files.

RESULTS

Age and race

The age range of the 10 subjects was from 27-40 years, with the mean and median ages being 34.3 and 34 years, respectively. Of these, 9 were Chinese and one was Indian, the other ethnic groups being unrepresented.

Parity

Nine subjects were multiparous, with between 2-4 previous pregnancies each (gravida: 3-5; para: 1-3). Of these, 5 had 3 previous pregnancies. Only one subject was primiparous.

Obstetric history

Seven subjects had uneventful antenatal histories with respect to the pregnancies associated with amniotic fluid embolism. Each of the 3 remaining cases presented with premature rupture of the gestational membranes, pre-eclampsia with diminished foetal movements and maternal pyrexia respectively.

Of the 9 multiparous subjects, 6 had uneventful past pregnancies, with 2 having had between 1-2 terminations previously, and the remaining subject having had 2 previous intra-uterine deaths, each on a separate occasion.

Clinical presentation of amniotic fluid embolism

Five subjects presented with dyspnoea (with or without cyanosis) and hypotension of sudden onset during labour, these being preceded by chest pain in one case. The remaining 5 cases presented with generalised convulsions, in the absence of any pregnancy-related hypertensive disorder. In all of these cases, the

sudden clinical deterioration was quite unexpected.

Seven subjects showed clinical evidence of coagulopathy, comprising 6 cases of disseminated intravascular coagulation (of which 3 cases were corroborated by post-mortem histological examination), while one presented with prolonged whole blood clotting time.

In 8 subjects, the clinical onset occurred during the first stage of labour, with each of the remaining cases occurring during the second and third stages respectively. The survival time (the period from initial presentation to the time death was formally pronounced) ranged from 1.5-106 hours, the median duration being 3 hours.

Obstetric procedures

Labour was induced in 3 subjects, while another 3 had augmentation of labour (artificial rupture of membranes, with or without intravenous oxytocin). Two subjects had forceps-assisted delivery and 5 underwent emergency caesarean sections following clinical onset of amniotic fluid embolism. In 2 subjects, post-partum total hysterectomy was performed for uterine atony and post-partum haemorrhage respectively.

Gestation and outcome of pregnancies

The gestational period ranged from 36 to over 40 completed weeks of amenorrhoea, the average gestation being 38.5 weeks. All cases involved singleton pregnancies. There were 6 male and 4 female foetuses, of which 9 were full-term and apparently normal, while one was delivered at 36 weeks. Eight were delivered, either vaginally or by means of caesarean section, of which 5 were live-births (one of which died 3 days later), comprising 2 males and 3 females; while 3 were still births, comprising 2 males and one female. Two male foetuses were found dead in-situ.

Gross Pathology

Lungs

Nine subjects showed pulmonary oedema, this being severe in 8 cases. The combined weights of the lungs ranged from 570-1,640g, the average weight being 979 g. In 6 cases, there was evidence of pulmonary haemorrhage, of which 3 were in the form of subpleural petechiae, the remaining 3 presenting as focal intra-parenchymal haemorrhage. Pulmonary collapse was noted in 2 cases, while severe bronchopneumonia was found in one subject who survived for over 4 days after the initial event.

Heart

In 3 cases, there were no gross cardiac pathology. However, 6 subjects showed evidence of mild coronary anteroma, although the coronary arteries were patent. Three showed subendocardial haemorrhage (a reflection of systemic shock), while one case presented with pericardial petechial haemorrhage.

Liver

In 6 cases, the liver showed hepatic congestion, fatty change, or both.

Reproductive tract

Significant utero-cervical injury was found in 3 cases, comprising a case of severe bilateral utero-cervical lacerations, another of a right lateral utero-cervical rupture and one of a right postero-lateral cervical laceration.

The remaining organs showed no significant gross pathology.

Histopathology

In all 10 cases, squamous epithelial emboli were detected in the pulmonary vasculature, with one of these also showing the presence of mucin. Squamous epithelial cells were present in the renal vasculature in 2 cases, while in one case, they were also found in the blood vessels of the myometrial interstitium and at the edge of a utero-cervical laceration.

Mixed inflammatory infiltrates were present within the alveolar spaces in 2 cases, while in another 2, there was evidence of similar pulmonary interstitial, perivascular and peribronchiolar inflammation.

Focal myocardial necrosis was present in one case, while another showed evidence of interstitial mononuclear inflammatory infiltrates within the myocardium.

Focal hepatocellular necrosis was found in one case. In 3 cases, fibrin microthrombi (consistent with disseminated intravascular coagulation) were present in the pulmonary vasculature.

DISCUSSION

Amniotic fluid embolism is thought to arise from the entry of amniotic fluid into the maternal circulation, as a result of a tear in the placental membranes and rupture of the uterine, placental or cervical veins of the female genital tract. Theoretically, this could be related to a vaginal or cervical laceration, a uterine rupture, a caesarean section wound, or following placental abruption. It may even occur following the normal separation of the placenta[5].

Consequently, epithelial squames from the foetal skin, lanugo hair, vernix caseosa, mucin from the foetal respiratory and gastrointestinal tracts and, occasionally, bile from meconium contamination of the amniotic fluid, enter the maternal circulation and may be found in the patient's pulmonary microcirculation on post-mortem examination[6-10], a feature that was found in all 10 cases studied. In particular, the presence of epithelial squames in the pulmonary vasculature, when interpreted in the appropriate clinical context, is highly diagnostic[4,11-14].

It appears that amniotic fluid embolism is related to increasing age and parity[15], an observation which concurs with the results of the present study. Indeed, it has been postulated that both these conditions predispose to the spontaneous rupture of the gestational membranes which tend to be weaker in older and multiparous women[16].

Traditionally, the acute effects of amniotic fluid embolism were regarded as being purely obstructive in nature[4]. Thus, the occlusion of the pulmonary vasculature by foetal debris was thought to cause pulmonary hypertension and consequent acute right ventricular failure[4, 17, 18]. However post-mortem examination has repeatedly demonstrated a poor correlation between the amount of amniotic fluid debris found in the vessels and the rapidity of the fatal course[9, 10, 19]. Furthermore, the conventional haemodynamic alterations presumably engendered by the entry of amniotic debris into the pulmonary vasculature were results produced experimentally in animals and subsequently extrapolated to human beings, when in fact, left ventricular failure is the only haemodynamic abnormality consistently observed in humans[9, 10, 19].

Current theories are centred around a biphasic pathophysiological response, beginning with an initial phase of intense pulmonary vasospasm caused by the presence of amniotic fluid, resulting in severe pulmonary hypertension and marked hypoxia. This transient stage is responsible for about 50% of deaths during the first hour[10, 20], which is in accord with the rapidity with which death occurred in 9 of the cases reviewed. Acute left ventricular failure then ensues, this being attributed either to profound hypoxia or to a direct depressant effect of the contents of the amniotic fluid on the myocardium[21]. Further, experimental evidence indicates that coronary artery perfusion may be decreased in amniotic fluid embolism[14, 22].

Severe pulmonary oedema is observed in up to 70% of cases. However, part of it is non-cardiogenic in origin and is thought to be related to increased permeability of the damaged alveolar-

capillary membrane[3].

To further complicate matters, an anaphylactic response has been observed in amniotic fluid embolism, possibly involving leuctorienes, these being mediators of immediate hypersensitivity reactions[23]. In fact, leucotrienes and prostaglandins are present in amniotic fluid in increased concentrations during labour[24]. Other endogenous mediators, such as proteolytic enzymes, histamine and serotonin have also been implicated[17].

Disseminated intravascular coagulation develops in about 40% of the survivors in the first phase, this being, in part, a secondary coagulopathy engendered by the initial haemodynamic turbulence[10,25,26]. Also, amniotic fluid has been shown to shorten whole blood clotting time, display thromboplastic-like properties, induce platelet aggregation, promote the release of platelet factor III and activate Factor X, as well as the complement cascade, in-vitro. In addition, trophoblastic tissue, which may be present in amniotic fluid, is known to have strong thromboplastin effects[27-29] and may, thus, contribute substantially to the development of disseminated intravascular coagulation[4], which was a common observation in the cases reviewed.

It has been further postulated that this condition may well be caused by the infusion of abnormal amniotic fluid into the maternal circulation, as the introduction of normal amniotic fluid into the maternal circulation is probably harmless[10].

Post-mortem examination

Fatal amniotic fluid embolism can only be conclusively established at autopsy and this depends heavily upon the histological demonstration of foetal debris, mainly within the pulmonary vasculature.

Epithelial squames may be demonstrated by routine haematoxylin and eosin staining and confirmed with phloxine-tartrazine which confers a bright red colour upon keratin squames. Phloxine also stains erythrocytes and viral inclusions positively and in a similar manner, and morphological discrimination between these elements may be necessary, although this should not be difficult. Other stains such as Alcian-Blue for mucin and Sudan Black or Oil Red-O for vernix may also be employed[30,31]. The detection of foetal isoantigens and of human keratin in maternal tissues, via immunoperoxidase methods[13, 32], have recently been used in the diagnosis of amniotic fluid embolism.

In cases where disseminated intravascular coagulation has supervened, the presence of fibrin thrombi in the microvasculature of the lungs and in the other viscera such as the kidneys, liver, spleen and the brain should be sought for, aided by special stains such as Martier's Scarlet Blue or phosphotungistic acid-haematoxylin (PTAH).

As intravascular epithelial squames may be scarce, and extensive tissue sampling, particularly of the lungs, is necessary. Indeed, amniotic fluid has a significant content of particulate material only in the last month of pregnancy[33].

It should be noted that small-scale, asymptomatic embolisation of foetal squamous cells has been postulated to occur, this being akin to the well established observation that trophoblastic cells are commonly found in the maternal venous circulation without adverse effects[34-37]. Therefore, the presence of foetal elements in the pulmonary vasculature must be interpreted in the context of the clinical presentation, as illustrated by the present study. Other possibilities, such as septic shock, aspiration, pneumonitis, acute myocardial infarction, pulmonary thromboembolism and placental abruption should also be considered[10].

Clinical correlation

Typically, amniotic fluid embolism presents as dyspnoea, shock and cyanosis of sudden onset with rapid cardiovascular collapse and severe acute pulmonary oedema, occurring usually, although not exclusively, in an older, multiparous woman. These symptoms tend to occur during vigorous labour with hypertonic uterine contractions, although this is not a pre-requisite. It is said that placental abruption is present in 50% of cases and in 40% of these, foetal death would have occurred prior to the acute signs of amniotic fluid embolism. Grand mal convulsions may complicate the clinical picture [2,10]. The present study clearly demonstrates these features, together with poor foetal survival.

Apart from labour and delivery, the condition may also occur without warning in the immediate post-partum stage[4, 10]. Other situations in which it may arise include first and second trimester abortion[38,39], including hysterotomy and prostaglandin and saline-induced abortions[40-43]; uncomplicated second trimester pregnancy[44]; blunt abdominal trauma[45]; amniocentesis[5] and even castor oil ingestion for the induction of labour[12]. Occasionally, it may also occur during a caesarean operation[46]. The role of oxytoxic agents in the pathogenesis of amniotic fluid embolism is somewhat controversial.

Medico-legal aspects

There can be little doubt that sudden maternal death from amniotic fluid embolism, which usually occurs without warning, causes considerable distress to the victims' relatives. It constitutes an important matter for a thorough elucidation of the cause of death, if for no more a compelling reason other than ascertaining whether such deaths might have been preventable. Therefore, it is an issue of tremendous concern to the medical and nursing staff concerned.

The role of the pathologist in these deaths is to determine the cause of death, in order to advise his clinical colleagues appropriately and to assist the Coroner in arriving at a verdict. Post-mortem procedures in this area have been extensively reviewed[47, 48]. Obviously, his pathological findings may have a significant bearing on any subsequent civil action which may be undertaken against the members of the ward staff by the aggrieved relatives in cases where there are sufficient grounds to warrant a charge of medical negligence.

In such situations, the pathologist must remain impartial and objective in his assessment of the pathological findings. The success of any medico-legal investigation or inquiry depends to a large extent on the accuracy and completeness of the autopsy, histological and other laboratory reports. In all these matters, due confidentiality must be observed. This matter is of particular importance in certain countries such as the United Kingdom where confidential enquiries into maternal deaths are conducted on a triennal basis[49]. There is, at present, no equivalent procedure in Singapore, although, under our current medico-legal system, maternal deaths are reported to the Coroner as a matter of policy.

CONCLUSION

Amniotic fluid embolism is a rare cause of sudden, unexpected maternal death, which tends to occur during labour, but may also present post-partum. The present study confirms the established clinico-pathological features of this condition and demonstrates the role of the maternal autopsy in elucidating the cause of such deaths.

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