Amniotic fluid embolism
Management and pregnancy outcome in survivors

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Amniotic fluid embolus

- A rare, often fatal complication of pregnancy
- Sudden cardiovascular collapse
- Altered mental status
- Disseminated intravascular coagulation
Historical perspective

- Fetal debris in pulmonary vasculature of a woman who died suddenly in labor
  - Meyer, 1926
- Death following sudden cardiovascular collapse in labor or the immediate postpartum period, fetal debris in pulmonary vasculature, defined as AFE
  - Steiner and Lushbaugh, 1941
Amniotic fluid embolism

- Research based on clinical series and autopsy results
- Still a significant contributor to maternal mortality
Pathophysiology

- Unclear
- Entry of amniotic fluid into maternal vasculature
- Obstruction of pulmonary vessels and cardiovascular collapse
- Anaphylaxis reaction to fetal material (mast cell degradation?)
- Complement activation? (Low C3, C4)
Anaphylactoid syndrome of pregnancy

- Entry of fetal antigens into the maternal circulation
- Abnormal activation of pro-inflammatory mediator systems
- Similar to systemic inflammatory response syndrome (SIRS)
Coagulopathy

- Unclear, probably multifactorial

- Amniotic fluid
  - Decreases whole blood clotting time
  - Induces platelet aggregation
  - Activates the complement cascade
Coagulopathy

- The presence of tissue factor in amniotic fluid activates the extrinsic pathway, triggers clotting by activating factor X, and consumption coagulopathy

- Furthermore, DIC may be secondary to complement activation
Inflammation / endothelial cell surface contact system

Entry of amniotic fluid into the maternal circulation

Kallikrein

Pre-kallikrein

the contact system

FXII

HMW-Kininogen

kinase II

Kinin

Coagulation

Complement activation

Vascular permeability

Anaphylactoid

C1q

C4

C3

plasmin

C3a → C5a

Kobayashi et al, Obstet Gynecol Surv 2015
Echocardiography

- Animal models, clinical cases
- Severe pulmonary hypertension
- Acute right ventricular failure
  - Dilated right ventricle with deviation of interventricular septum
  - Secondary left ventricular failure due to impaired left ventricular filling
Hemodynamic response

Biphasic:

- initial increase in pulmonary vascular resistance and right ventricular failure

And then -

- left ventricular failure
Amniotic fluid gains entry to maternal blood stream

- Mechanical block
- Pulmonary vessel obstruction

- Release of endogenous mediator
- Pulmonary vessel vasospasm
Clinical manifestation

- During labor and delivery or in the immediate postpartum
- Also following induced abortion, feticide, intrauterine procedures, etc
- 70% of cases before delivery

- Sudden cardiovascular collapse
- Profound hypotension
- Dyspnea or respiratory arrest
- Altered mental status
- Hemorrhage
Management

- Supportive care
- Maintenance of oxygenation, cardiac output and blood pressure
- Correction of coagulopathy
Epidemiology

- Estimated incidence of AFE
  - 1:15,000-1:53,000
  - Case fatality rate 13-30%
  - Perinatal mortality 9-44%

- Risk factors
  - Advanced maternal age
  - Placental abnormalities
  - Operative deliveries
  - Eclampsia
  - Polyhydramnios
  - Cervical lacerations and uterine rupture
Prognosis

- Improves with early diagnosis and aggressive treatment
- Of all affected patients, up to 50% die within the first hour
Time from onset until death

Yi Mu et al, BMC Pregnancy Childbirth 2016
Differential diagnosis

- Pulmonary thromboembolism
- Air embolism
- Anesthetic complication
- Drug-induced allergic anaphylaxis
- Myocardial infarction
- Cardiac arrhythmia
- Peripartum cardiomyopathy
- Aspiration of gastric content
- .....
Prognosis
Mortality

- Case-fatality rates have fallen:
  - 86% - 1979 Morgan case series
  - 61% - 1988-1994 Clark et al
  - 9-44% - 2000-2010 various series
Canadian database

- Population-based cohort study
- Canada, 1991/2-2008/9
- 4,508,462 deliveries
- 120 AFE cases
- Incidence 2.5:100,000
- Case fatality 27%

Kramer ET AL, BJOG 2012
Antepartum intrapartum and demographic dataset
US data

- Retrospective population-based study in California 2001-2007
- 3,556,567 deliveries
- 182 cases of AFE
- Incidence 5.1:100,000
- Case fatality 13.2%

Fong et al, J Mat Fet Neonat Med 2015
Australia-New Zealand prospective database

- AMOSS survey
- prospectively collected population-based study, 2010-2011
- 613,731 births
- 33 AFE cases, 5 deaths
- Incidence 5.4:100,000
- Case fatality 15.2%

McDonnell et al, BMC pregnancy childbirth 2015
Prognosis

- Improves with early diagnosis and aggressive treatment

- Of all affected patients, up to 50% die within the first hour

- Significant neurological morbidity among survivors
Prognosis
Neurological outcome

- Clark national registry (1988-1994) 46 women -
  - 61% neurological impairment
  - 50% in surviving infants

- UK registry (BJOG 2005) 31 women
  - 6% neurological impairment
  - 33 infants, 18% with HIE; 6% with CP
Diagnosis

- Amniotic fluid embolism is a clinical syndrome
- Clinical presentation
- Histopathologic confirmation not required
Clinical characteristics and risk factors
Prevalence of AFE by maternal age

Fong et al, J Mat Fet Neonat Med 2015
## Antepartum associations

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Condition absent</th>
<th>Condition present</th>
<th>Adjusted odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>3.1 (84)</td>
<td>272.6 (49)</td>
<td>69.9 (48.1–101.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disorders</td>
<td>4.7 (129)</td>
<td>1075.3 (4)</td>
<td>25.1 (8.6–73.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-existing renal disease</td>
<td>4.6 (128)</td>
<td>138.5 (5)</td>
<td>13.0 (5.2–32.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>4.5 (128)</td>
<td>57.4 (9)</td>
<td>7.0 (3.5–14.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Polyhydramnios</td>
<td>4.6 (126)</td>
<td>45.3 (6)</td>
<td>6.8 (3.0–15.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>4.7 (129)</td>
<td>36.9 (4)</td>
<td>5.8 (2.1–15.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.5 (123)</td>
<td>27.6 (10)</td>
<td>3.4 (1.8–6.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>4.6 (126)</td>
<td>21.1 (7)</td>
<td>1.8 (0.8–4.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Hypertensive disorders</td>
<td>4.3 (114)</td>
<td>18.9 (19)</td>
<td>2.2 (1.3–3.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>4.6 (126)</td>
<td>12.5 (7)</td>
<td>1.5 (0.7–3.3)</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>4.4 (115)</td>
<td>11.0 (18)</td>
<td>3.5 (0.4–30.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.4</td>
<td>10.6</td>
<td>1.5 (0.9–2.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>4.5</td>
<td>10.3</td>
<td>1.4 (0.8–2.3)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Fong et al, J Mat Fet Neonat Med 2015
### Late pregnancy/peripartum variables

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Prevalence of AFE (cases per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Condition absent</td>
</tr>
<tr>
<td>Amni infusion</td>
<td>4.6 (126)</td>
</tr>
<tr>
<td>Induction of labor</td>
<td>4.4 (107)</td>
</tr>
<tr>
<td>Post delivery curettage</td>
<td>4.7 (130)</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>4.6 (91)</td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td>4.4 (121)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>4.3 (116)</td>
</tr>
<tr>
<td>Peripartum cardiomyopathy</td>
<td>4.7 (130)</td>
</tr>
<tr>
<td>Low transverse cesarean delivery</td>
<td>2.3 (46)</td>
</tr>
<tr>
<td>Classical cesarean delivery</td>
<td>4.7 (129)</td>
</tr>
<tr>
<td>Mild preeclampsia</td>
<td>4.6 (125)</td>
</tr>
<tr>
<td>Severe preeclampsia</td>
<td>4.6 (127)</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>4.7 (130)</td>
</tr>
<tr>
<td>Death</td>
<td>4.1 (116)</td>
</tr>
</tbody>
</table>

Adjusted for: age, race, insurance status, diabetic disease, hypertensive disease; being adjusted is the morbidity itself.

Fong et al, J Mat Fet Neonat Med 2015
## Fetal/neonatal outcome

**Table 3. Fetal/infant outcomes among confirmed AFE cases**

(n = 120 for stillbirths, n = 54 for neonatal outcomes*)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (%)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>5 (4.2)</td>
<td>5.9 (2.0–17.4)</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>15 (27.8)</td>
<td>36.0 (18.6–69.7)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>17 (31.5)</td>
<td>11.8 (6.0–23.4)</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>5 (9.3)</td>
<td>5.0 (1.8–14.0)</td>
</tr>
<tr>
<td>Seizure</td>
<td>8 (14.8)</td>
<td>22.8 (9.7–53.3)</td>
</tr>
<tr>
<td>Jaundice (nonimmune haemolytic/traumatic)</td>
<td>9 (16.7)</td>
<td>1.4 (0.6–3.2)</td>
</tr>
<tr>
<td>Length of stay &gt;7 days</td>
<td>18 (33.3)</td>
<td>18.5 (8.5–40.2)</td>
</tr>
</tbody>
</table>

Kramer ET AL, BJOG 2012
Subsequent pregnancies

- Very few subsequent pregnancies in survivors have been reported in the literature

- Apparently not a recurrent disease
Sheba series

- Tertiary care medical center
- ~10,000 deliveries a year
- Over a 15 year period 2003-2017
- 13 cases identified with suspected AFE
- Incidence 8.7:100,000
Clinical presentation

- Sudden cardiovascular collapse
- Respiratory distress
- DIC

- 10 cases at term, during labor
  - 8 cases intrapartum, 5 induction of labor
  - 2 elective CS

- 3 cases fetal demise and uterine evacuation
2 serious maternal outcomes:
- Anoxic brain damage
- No maternal death
- No persistent cardiac dysfunction

Neonatal outcome: 10 cases
- APGAR score ≤ 7 in 7
- Neonatal acidosis 4
- Neonatal death – 0

3 fetal demise (17, 28, 20 weeks)
Subsequent pregnancies

- 10 subsequent pregnancies
  - 5 term AGA deliveries
  - 4 missed abortions
  - 1 EUP

- No recurrence of AFE
Amniotic fluid embolus

- Anaphylactoid syndrome of pregnancy
- Rare
- Management has improved with time
- Still a significant contributor to maternal mortality

- Integrated multidisciplinary care is the key to intact survival