Amniotic Fluid Embolism

C. David Adair, M.D.
PROFESSOR AND VICE-CHAIRMAN
DEPARTMENT OF OB/GYN
University of Tennessee College of Medicine
Chattanooga, TN
Disclosure

• I am Chairman, Founder, and Chief Science Officer for Glenveigh Medical. I led the development of Ebb and have financial interest in the product.

• I am major shareholder for Velo Bio and hold patent rights/Royalties for a Preeclampsia therapeutic and diagnostic. This has been optioned to AMAG Pharmaceuticals.

• Board Member for Amniotic Fluid Embolism Foundation.
Outline

- Background
- Incidence & Outcomes
- Pathophysiology & Etiology
- Diagnosis
- Evaluation & Treatment
- Summary
- Where have we been?
- Where do we go?
Learning Objectives

- Recognize clinical scenario
- Differential diagnosis consideration
- Review of AFE morbidity and mortality
- Management skill acquisition
Background
Historical References

Brazil-Medico

SODRE & Cla. – Editores
140, Rua do Rosario Rio de Janeiro
Caixa Potal 338 – End. Telegr. Brazmedico
EMBOLIA PULMONAR AMNIO-CASEOSA
Pelo Dr. J. R. Meyer

Brazil-Med 1926; 40 (11): 301-303

MATERNAL PULMONARY EMBOLISM
BY AMNIOTIC FLUID
AS A CAUSE OF OBSTERIC SHOCK AND UNEXPECTED DEATHS IN OBSTETRICS
PAUL E. STEINER, M.D., Ph.D.
AND
C.C. LUSHBAUGH, B.S.
CHICAGO

JAMA 1941; 117: 1245-1254 & 1341-1345
A Syndrome - Definition
Clinical Presentation

• Classic triad:
  o Hypoxia
  o Hypotension or hemodynamic collapse
  o Coagulopathy

• Remains poorly understood: unpredictable, rare, acute, and lacks a gold standard diagnosis

• There probably are formes frustes of AFE

• “Let us be careful not to make it a waste basket for all cases of unexplained death in labor…”

  Eastman, 1948
Incidence & Outcomes
Incidence

- Incidence (per 100,000 maternities)
  - Australia, Canada, the Netherlands, UK & USA
  - Retrospective discharge database
    - ~1:17,000
  - Validated case identification
    - ~1:45,000

If the difference between the above 2 rates is due solely to false positives in the former, the incidence of AFE is overestimated by 65% in retrospective discharge database studies. (GA DILDY)

<table>
<thead>
<tr>
<th>Country</th>
<th>Time period</th>
<th>Publication</th>
<th>Contribution to maternal Mortality (%)</th>
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<tbody>
<tr>
<td>Sweden</td>
<td>1951-1980</td>
<td>Hogberg, 1985</td>
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<td>USA</td>
<td>1979-1986</td>
<td>Atrash, 1990</td>
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<td>Australia</td>
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<td>Singapore</td>
<td>1990-1999</td>
<td>Lau, 2002</td>
<td>31</td>
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<tr>
<td>USA</td>
<td>2000-2006</td>
<td>Clark, 2008</td>
<td>14</td>
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### HCA, 2000-2006

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<tr>
<th>CAUSE OF DEATH</th>
<th>Number</th>
<th>%</th>
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<tr>
<td>Complications of Preeclampsia</td>
<td>15</td>
<td>16</td>
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<tr>
<td>Amniotic fluid embolism</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Obstetric hemorrhage</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>10</td>
<td>11</td>
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<tr>
<td>Pulmonary Thromboembolism</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Non-obstetric infection</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Obstetric infection</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Accident/suicide</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Medication error or Reaction</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Other</td>
<td>11</td>
<td>12</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>95</td>
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<table>
<thead>
<tr>
<th>Publication</th>
<th>Years</th>
<th>Population</th>
<th>Methodology</th>
<th>AFE(N)</th>
<th>MM(%)</th>
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<tbody>
<tr>
<td>Morgan 1979</td>
<td>1941-1978</td>
<td>English lit.</td>
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<td>272</td>
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<td>Clark 1995</td>
<td>1983-1994</td>
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<td>Registry</td>
<td>46</td>
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<td>Tuffnell 2005</td>
<td>1997-2004</td>
<td>UK</td>
<td>Registry</td>
<td>44</td>
<td>30</td>
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<td>Knight 2010</td>
<td>2005-2009</td>
<td>UK</td>
<td>UKOSS</td>
<td>60</td>
<td>20</td>
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<td>Stolk 2012</td>
<td>2004-2006</td>
<td>Netherlands</td>
<td>Registry</td>
<td>9</td>
<td>11</td>
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<td>Guillaume 2013</td>
<td>2000-2010</td>
<td>France</td>
<td>Chart Review</td>
<td>11</td>
<td>27</td>
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</table>
Pathophysiology
Proposed Pathophysiology

Anaphylaxis (IgE)  
Sepsis (Endotoxin)  
Amniotic Fluid Embolism (various fetal elements)

Endogenous Mediator Release

Clinical Manifestations

Proposed Pathophysiology

• Phase I
  o Vasoactive Substance(s)
  o Pulmonary vasospasm
  o Profound hypoxia
    • Pulmonary injury
    • Myocardial injury
  o Resolution in 15-30 min

• Phase II
  o Left heart failure
  o Pulmonary edema/ARDS
  o Coagulopathy
Clark et al. Hemodynamic alterations associated with amniotic fluid embolism: a reappraisal.

Coagulopathic Process

• Animal studies – Inconsistent results
• In vitro studies amniotic fluid:
  o Shortens whole blood clotting time
  o Has thromboplastin-like effect
  o Induces platelet aggregation & release of platelet factor III
  o Activates complement cascade
  o Contains a direct factor X activating factor
• Human studies
  o AFE coagulopathy probably similar to that in severe placental abruption
Maternal Death Following Cardiopulmonary Collapse After Delivery: Amniotic Fluid Embolism or Septic Shock Due to Intrauterine Infection?

Roberto Romero¹,², Nicholas Kadar, Edi Vaisbuch ¹,³, Sonia S. Hassan ¹,³

- 2 cases of maternal death attributed to AFE
- Supra-lethal levels maternal plasma TNF-α (>0.1 ng/mL) at admission
  - 29 yo G3P1 at 41+ weeks 1 ng/mL
  - 30 yo G3P2 at 28+ weeks 10 ng/mL

As illustrated in this case, uterine hypertonicity followed the initial signs and symptoms of AFE.

Induction of Labor?

  - Canada 1991-2002
  - Association: yes

  - USA 1999-2003
  - Association: no

- Knight et al. *Obstet Gynecol* 2010
  - UK 2005-2009
  - Association: yes
• Prepidil Package Insert (02/09)
  o “The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).”

• Cervidil Package Insert (04/10)
  o “The Clinician should be alert that use of dinoprostone may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).”
Diagnosis
Diagnostic Criteria

Either - In the absence of any other clear cause
Acute maternal collapse with one or more of the following
   Acute fetal compromise
   Cardiac arrest
   Cardiac arrhythmias
   Hypotension
   Maternal hemorrhage
   Coagulopathy
   Premonitory symptoms
   Seizure
   Shortness of breath

Excluding women with maternal hemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardio-respiratory compromise

Or

Women in whom the diagnosis was made at postmortem examination with fetal squames or hair in the lungs

Diagnostic Criteria

• AFE Registry Entry Criteria
  o Acute hypotension or cardiac arrest
  o Acute hypoxia
  o Coagulopathy
  o Onset during labor, delivery, or 30 minutes postpartum
  o Absence of any other explanation

Differential Diagnosis

- Acute myocardial infarction
- Anaphylactic shock
- Anesthetic accident
- Aspiration pneumonia
- Placental abruption
- Pulmonary thromboembolism
- Septic shock
Histologic Findings of AFE
Treatment & Management
Initial Evaluation

- CBC & platelet count
- Fibrinogen and FSP
- PT, PTT, and INR
- Blood type & cross
- Arterial blood gas
- Red top hold

- Serum electrolytes
- Cardiac enzymes
- Chest x-ray
- 12-lead EKG
- Echocardiogram
Treatment

- Initial treatment is largely supportive of end organs
- CPR, high FiO2
- Treat left ventricular failure
  - Volume expansion, inotropes
- Fetal management
  - Cardiac arrest: perimortem C/S ≤ 5 minutes
    - ABC’s + D (delivery)
  - Hemodynamically unstable: individualize support
Treatment: case reports

- Cardiopulmonary bypass
- Hemofiltration
- Recombinant Factor Vlla
- Nitric oxide
- High-dose corticosteroids
Simulation & Team Training


Recurrence Risk

<table>
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<tr>
<th>Year</th>
<th>Author</th>
<th>Journal</th>
<th>Numerators</th>
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<tbody>
<tr>
<td>1992</td>
<td>Clark</td>
<td>AJOG</td>
<td>0/2</td>
</tr>
<tr>
<td>1995</td>
<td>Burrows</td>
<td>ANZJOG</td>
<td>0/1</td>
</tr>
<tr>
<td>1998</td>
<td>Duffy</td>
<td>AIC</td>
<td>0/2</td>
</tr>
<tr>
<td>1998</td>
<td>Collier</td>
<td>AIC</td>
<td>0/1</td>
</tr>
<tr>
<td>2000</td>
<td>Stiller</td>
<td>JRM</td>
<td>0/1</td>
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<tr>
<td>2005</td>
<td>Demianczuk</td>
<td>JOGC</td>
<td>0/1</td>
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<tr>
<td>2006</td>
<td>Abecassis</td>
<td>IJOA</td>
<td>0/1</td>
</tr>
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</table>

Maximum Risk with 95% CL: “Rule of 3” (3/n)*100 = 33%

Where do we go?

Objective – To develop a UK-wide Obstetric Surveillance System to describe the epidemiology of a variety of uncommon disorders of pregnancy.

Mission – to improve the care given to women, their babies and their families, by advancing knowledge and contributing to the evidence base about serious, rare disorders in pregnancy including near-miss events, through international co-operation and collaborative working.

Mission - AFE Foundation exists to spur clinical research, raise awareness, provide clinical and patient based information and offer supportive services to those affected by or interested in Amniotic Fluid Embolism.

https://www.npeu.ox.adc.uk/ukoss

http://www.npeu.ox.ac.uk/inoss

http://www.afesupport.org
AFE Registry at BCM

- AFE Foundation & BCM partnered to create a new registry
  - The AFE Registry opened 2 August 2013
  - Cases are collected and abstracted
  - Cases are categorized (Classic v Atypical v Unlikely AFE)

- Future Plans
  - AFE families Bio-Bank (store serum/plasma and DNA)
  - Network for collection of specimens from acute AFE cases
Recombinant Factor VII Algorithm

- Diagnosis of severe PPH
- All therapies attempted
- Sustained bleeding
- 90 μg/kg i.v. bolus over 3-5 min)
- Sustained bleeding after 20 min
- Second dose
- Hysterectomy
Massive Transfusion Protocol

- 6 RBC
- 6 FFP
- 6 Platelets
- 1 Factor 7
- Repeat
New or Theoretical Developments

• Liquid or “Thawed Plasma”
• Plasma from Whole Blood expires approximately 5 days before the 35 days of whole blood
• This is in contrast to FFP up to 1 year (40 minute thawing)
• “Endotheliopathy” of trauma
• University of Texas Houston Trauma
New or Theoretical Developments

- Thromboelastogram (TEG)
- I-stat
- Cell Saver
- Vacuum Attachment D&E, Wall Suction
- Intrauterine Infusion of Prostaglandins (Not FDA cleared)

- C Georgiou: Hypertension Research in Pregnancy 2014;2:1-10
• RCT of TXA for PPH
• Ongoing
• 13,000 enrolled
• Planned 15,000
Kcentra (Four Factor Prothrombin Complex Concentrates)

- FDA approval for Suprathreshold INR
- Vitamin K antagonists, coumadin, Apixaban (oral agonists)
- ? DVT Best evidence says No
- $$$$$$$ 15 to 20 K
New or Theoretical Developments

- Thromboelastogram (TEG)
- I-stat
- Cell Saver
- Vacuum Attachment D&E, Wall Suction
- Tranexamic Acid - EU Trials are encouraging (small #)
- Woman Trial Clinical trials.gov ID: NCT00872469
  - 15,000 patients to 4% to 3% or death or hysterectomy

- C Georgiou: Hypertension Research in Pregnancy 2014;2:1-10
POSTPARTUM HEMORRHAGE
Compression Suture

Technique:

Ethicon 48 G (Urology)
82 mm tapered needle
70 cm #1 or 2 chromic or vicryl
Uterine Sandwich
Ligasure
LigaSure

- Pressure + energy for tissue fusion
- Permanently fuses vessels to 7mm
- Seal cycle 2-4 seconds
- Automatically stops when seal complete
Summary
Summary

- Thought to follow maternal exposure to fetal antigens
- Pathophysiology similar to anaphylaxis & septic shock
- Treatment is generally supportive
- Maternal-fetal morbidity & mortality frequent
- OB teams should be prepared for acute emergencies
- Team training & simulation training may be helpful
- Better predictive and diagnostic tests are needed
- Current efforts are being invested in improved diagnostic tests and treatment
- Simulation allows for massive blood transfusions and AFE

All recommendations GRADE 1C
Key Facts to Take Home

- 1/8,000 to 1/80,000 deliveries
- Maternal mortality up to 86%,
- A leading cause of U.S. maternal mortality
  - 11-14% of all maternal deaths
  - Most common cause of peripartum death
  - 2-8 per 100,000
  - 7.5 to 10% of all maternal deaths
  - Mortality approaches 80%, U.S. Registry 61%
  - Survivors 7 to 10% neurological impairment
The CMQCC Staged Approach

- Stage 0 – Active management 3\textsuperscript{rd} stage
- Stage 1 – EBL limits exceeded, stable
- Stage 2 – Continued bleeding, unstable
- Stage 3 – Major obstetric hemorrhage
  - EBL > 1500, unstable, coagulopathy

Mhyre J. Anesth 2011
Modified Early Obstetric Warning Scores (MEOWS)\textsuperscript{1}

Contact a physician for early intervention if the patient scores ≥2 at any time: Anesthesiology 2011, ASA Annual Meeting; Rath. Acta Obstetricia et Gynecol Scandinavica 2011

<table>
<thead>
<tr>
<th>Score</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>Pulse</td>
<td>≤40</td>
<td>41-50</td>
<td>51-100</td>
<td>101-120 or 10-20% increase</td>
<td>&gt;120 or &gt;20% increase</td>
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<tr>
<td>SBP</td>
<td>≤85 or &gt;20% decrease</td>
<td>85-100</td>
<td>101-150</td>
<td>151-160</td>
<td>&gt;160</td>
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<tr>
<td>DBP</td>
<td>&lt;45</td>
<td>45-80</td>
<td>81-100</td>
<td>&gt;100</td>
<td></td>
</tr>
<tr>
<td>SpO2</td>
<td>&lt;95%</td>
<td>95-100%</td>
<td></td>
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<tr>
<td>RR</td>
<td>≤10</td>
<td>11-20</td>
<td></td>
<td>21-30</td>
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<tr>
<td>Temp</td>
<td>≤35.0</td>
<td>35.1-35.9</td>
<td>36.0-37.9</td>
<td>≥38.0</td>
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<tr>
<td>CNS</td>
<td>Normal</td>
<td>Responds</td>
<td></td>
<td>Pain response</td>
<td></td>
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<tr>
<td>Blood Loss (%)</td>
<td>Blood Pressure</td>
<td>Signs &amp; Symptoms</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>----------------</td>
<td>----------------</td>
<td>------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500-1000ml (10-15)</td>
<td>normal</td>
<td>Palpitations, dizziness, tachycardia</td>
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<tr>
<td>1000-1500ml (15-25)</td>
<td>Slightly low</td>
<td>Weakness, sweating, tachycardia</td>
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<tr>
<td>1500-2000ml (25-35)</td>
<td>70-80</td>
<td>Restlessness, pallor, oliguria</td>
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<tr>
<td>2000-3000ml (35-45)</td>
<td>50-70</td>
<td>Collapse, air hunger, anuria</td>
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</table>

>2.5 l blood loss – 50% mortality if not managed urgently appropriately
a wide array of therapies for postpartum hemorrhage

 disappointing that a major failure in three of the five women who died ........... a failure to appreciate that bleeding was occurring.”
## Additional signs and symptoms of severe obstetric hemorrhage

*Anesthesiology* 2011, ASA Annual Meeting

<table>
<thead>
<tr>
<th>Physical Signs</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Narrow pulse pressure</td>
<td>Anxiety, restlessness, confusion</td>
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<tr>
<td>Pallor, mottled appearance</td>
<td>Palpitations, dizziness, diaphoresis</td>
</tr>
<tr>
<td>Cold and clammy extremities</td>
<td>Hunger for air</td>
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<tr>
<td>Oliguria &lt;0.5mL/kg/hr</td>
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</table>
## Postpartum Hemorrhage Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Blood loss (ml)</th>
<th>% Loss</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>1</td>
<td>&lt; 900</td>
<td>&lt; 15</td>
<td>Few signs</td>
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<tr>
<td>2</td>
<td>1,200 – 1,500</td>
<td>20 - 25</td>
<td>Orthostasis</td>
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<tr>
<td>3</td>
<td>1,800 – 2,100</td>
<td>30 - 35</td>
<td>Hypotension</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 2,400</td>
<td>&gt; 40</td>
<td>Shock</td>
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