Labor Epidurals and Maternal Fever: Fact vs. Fiction

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Pre-presentation Survey

How many audience members believe that epidural labor analgesia *is associated with* maternal fever?
Talk Overview
Fever and Epidural

• Critically review literature
• Review consequences
• Theorize mechanisms
• Discuss prevention & treatment
• Propose next steps in studying the association
Fever and Epidural
Studies examining the association

- Observational (women choose their analgesia)
  - Retrospective
  - Prospective

- Randomized Controlled
  - Randomized to epidural vs IV opioid for either:
    - The entirety of labor
    - Early versus late in labor

- Before-and-After
  - Epidurals are introduced into a practice
MATERNAL PYREXIA ASSOCIATED WITH THE USE OF EPIDURAL ANALGESIA IN LABOUR

LUCA FUSI
MICHAEL J. A. MARESH*

PHILIP J. STEER
RICHARD W. BEARD

THE LANCET, JUNE 3, 1989

Fig 1—Mean vaginal temperature (°C) in the two groups of patients during labour.

●, Pethidine group; ○, epidural analgesia group; vertical bars, SEM.
MATERNAL TEMPERATURE REGULATION DURING EXTRADURAL ANALGESIA FOR LABOUR

W. R. CAMANN, L. A. HORTVET, N. HUGHES, A. M. BADER AND S. DATTA

Fig. 2. Mean (SE) tympanic temperatures during labour in the extradural–BF (○), extradural–B (X) and opioid (■) groups. $P < 0.01$: **compared with extradural–BF and extradural–B groups; ††compared with pre-extradural temperature (ANOVA).
# Incidence of fever *with* versus *without* epidural

**Observational studies**

<table>
<thead>
<tr>
<th>Study author</th>
<th>Year</th>
<th>Fever Definition (°C)</th>
<th>Epidural group [% (n/N)]</th>
<th>Non-epidural group [% (n/N)]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vinson</td>
<td>1993</td>
<td>≥37.5, &gt;38</td>
<td>26.8 (11/41), 14.6 (6/41)</td>
<td>8.3 (3/36), 0 (0/36)</td>
<td>.05, .03</td>
</tr>
<tr>
<td>Herbst</td>
<td>1995</td>
<td>≥38</td>
<td>6.4 (44/683)</td>
<td>1.1 (28/2426)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ploeckinger</td>
<td>1995</td>
<td>&gt;38</td>
<td>1.6 (17/1056)</td>
<td>0.2 (11/6261)</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Lieberman</td>
<td>1997</td>
<td>&gt;38</td>
<td>14.5 (152/1047)</td>
<td>1.0 (6/610)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mayer</td>
<td>1997</td>
<td>≥37.8</td>
<td>20.4 (39/191)</td>
<td>2.1 (2/96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dashe</td>
<td>1999</td>
<td>≥38</td>
<td>46.3 (37/80)</td>
<td>26.1 (18/69)</td>
<td>.01</td>
</tr>
<tr>
<td>Kaul</td>
<td>2001</td>
<td>&gt;38</td>
<td>6.6 (61/922)</td>
<td>0 (0/255)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adakidis</td>
<td>2011</td>
<td>≥38</td>
<td>11 (54/480)</td>
<td>0.8 (4/480)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Riley</td>
<td>2011</td>
<td>&gt;38</td>
<td>22.7 (34/150)</td>
<td>6.0 (3/50)</td>
<td>.009</td>
</tr>
</tbody>
</table>
Clear conclusion from this table:

Women who choose epidural labor analgesia are more likely to develop a fever than women who do not.
Problems with observational studies

• Selection Bias
  • Infected women (chorioamnionitis) have painful labors
  • Long, complicated labors require epidurals

• Obstetric practice influenced
  • Obstetricians NOT blinded
    • More manual exams?
    • Greater oxytocin administration?
Problem in Observational Studies:

“An Averaging Artifact”
Maternal tympanic temperature in the 4 hours immediately after initiation of epidural analgesia, stratified by ultimate intrapartum fever status. Temperature points that are **significantly different** between the two curves are marked (repeated measures analysis * P+ P++ PP=.26

Intrapartum Epidural Analgesia and Maternal Temperature Regulation.
Goetzl L, Rivers J, Zighelboim I, Wali A, Badell M, Suresh M.
"The Averaging Artifact":

Intrapartum Epidural Analgesia & Maternal Temperature Regulation.

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Fig 1—Mean vaginal temperature (°C) in the two groups of patients during labour.

●, Pethidine group; ○, epidural analgesia group; vertical bars, SEM.
Measured temperature slope before & after epidural
An exoneration of the association?

Epidural Analgesia Not to Blame for Fever in Laboring Women, Study Suggests

July 25, 2012 — A study from the August issue of UAB News says epidurals do not cause fever in women in labor.

Determine study eligibility. We excluded patients with medical conditions that would affect temperature regulation or the normal course of labor, particularly chorioamnionitis. Patients who received medications known to affect body temperature (acetaminophen, prostaglandin, or ibuprofen), and patients with active cardiac, pulmonary, or neurologic disease were also ineligible. The diagnosis of chorioamnionitis was based on a combination of fever (temperature more than 38.0°C) or a combination of at least two of the following findings: significant maternal tachycardia (more than 160 bpm), purulent or foul-smelling amniotic fluid or vaginal discharge, uterine tenderness, or maternal leukocytosis (total blood leukocyte count more than 18,000 cells/μl). Obstetric indications for labor (nulliparity and gestational age for age) were included.

Once enrolled, we entered data into the database. Each patient received a unique identifier, and all data were recorded. Data collection included the following: maternal age, BMI, parity, gestational age, delivery mode, type of anesthesia, and complications.

Materials and Methods

Design
The Institutional Review Board of the University of Alabama at Birmingham (Birmingham, Alabama) approved this study. After obtaining written informed consent, 90 women were recruited at University of Alabama at Birmingham’s Women and Infants Center from November 2008 to September 2010. Patients were divided into two groups: operative and nonoperative. The operative group included women who had cesarean delivery, and the nonoperative group included women who delivered vaginally. Women were then assigned to one of two groups: those who received epidural analgesia and those who did not. Data collection included the following: maternal age, BMI, parity, gestational age, delivery mode, type of anesthesia, and complications.
Maternal tympanic temperature in the 4 hours immediately after initiation of epidural analgesia, stratified by ultimate intrapartum fever status. Temperature points that are **significantly different** between the two curves are marked (repeated measures analysis * P+ P++ PP=.26

**Intrapartum Epidural Analgesia and Maternal Temperature Regulation.**

Goetzl L, Rivers J, Zighelboim I, Wali A, Badell M, Suresh M.

Conclusions from Goetzl & Frolich's work:

- **Previous thought:**
  - All women with epidural had gradual temperature elevation.

- **Current thought:**
  - ~20% have robust, immediate fever
  - ~80% remain afebrile

- **Excluding any women who becomes febrile:**
  - Excluded ~20% that needs to be studied
  - Revealed ~80% do not have temp increase with epidural (already known)
Conclusion from Observational Studies:

Women who choose epidural labor analgesia are more likely to get a fever.

Question from Observational Studies:

Does epidural labor analgesia cause fever?

Association ≠ Causation
Incidencia de fiebre con versus sin epidural laboral. Estudios Controlados Aleatorizados

<table>
<thead>
<tr>
<th>Estudio autor</th>
<th>Año</th>
<th>Diseño</th>
<th>Definición de fiebre (°C)</th>
<th>Grupo epidural [% (n/N)]</th>
<th>Grupo no epidural [% (n/N)]</th>
<th>P-valor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramin</td>
<td>1995</td>
<td>RCT: *Datos analizados para mujeres protocolo cumplidores solo</td>
<td>≥38</td>
<td>22.7 (98/432)</td>
<td>4.8 (21/437)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sharma</td>
<td>1997</td>
<td>RCT</td>
<td>&gt;38</td>
<td>23.9 (58/243)</td>
<td>6.2 (16/259)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lucas</td>
<td>2001</td>
<td>RCT: Todos los pacientes tenían membranas rotas &gt;6 h. Incluyó fiebre hasta 6 h postparto</td>
<td>≥38</td>
<td>20.4 (76/372)</td>
<td>7.1 (26/366)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sharma</td>
<td>2002</td>
<td>RCT: *Datos analizados para mujeres protocolo cumplidores solo</td>
<td>≥38</td>
<td>33.2 (75/226)</td>
<td>6.9 (16/233)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>De Orange</td>
<td>2011</td>
<td>RCT: Pacientes con analgesia combinada-spinal vs analgesia no farmacológica =38</td>
<td>14.3 (5/35)</td>
<td>0 (0/35)</td>
<td>.027</td>
<td></td>
</tr>
</tbody>
</table>

Problems with RCTs

• Drop-out and Cross-over:
  • Complicated, infected labors cross-over epidural group
  • Fast, easy labors cross-over to non-epidural group
  • Not all analyzed as intention-to-treat

• Obstetric practice may be influenced
  • Obstetricians cannot be blinded

• Only 1 of 5 RCTs had fever as primary outcome
Before-and-After Study

Retrospective cohort 1 yr before VS 1 yr after epidural service.

- **BEFORE:** <1% epidural
- **AFTER:** 83% epidural

Relative Risk = 18.3, 95% CI 5.8, 57.8; P < .01
Observational, randomized-controlled, and before-and-after designed studies all support the association between epidural labor analgesia and fever.

*How else can we assess for causation?*

*Is there a dose effect?*
Early vs Late CSE Labor Analgesia

Wong 2005, n = 750

EARLY (<4cm dilation)
• 440 minutes
• $T_{\text{MAX}}$ 37.3 ± 0.5°C

LATE (≥4cm dilation)
• 330 minutes
• $T_{\text{MAX}}$ 37.3 ± 0.5°C

Difference in neuraxial analgesia length
• $p < 0.001$

No $T_{\text{MAX}}$ difference between groups
• $p = 0.06$

Early vs Late Epidural Labor Analgesia

Wang 2009, n = 12,793

EARLY (<4cm dilation)
- 12.6 hours
- $T_{AVG} \ 37.4 \pm 0.4^\circ C$

LATE (≥4cm dilation)
- 4.8 hours
- $T_{AVG} \ 37.2 \pm 0.4^\circ C$

• No difference in $T_{AVG}$: $p = 0.52$

Conclusion: There is no “dose-effect”

The longer a woman has a labor epidural does not increase her likelihood of developing an intra-partum fever...
Does Epidural Labor Analgesia Cause Intrapartum Fever?

YES

- Many Observational Studies
- 5 Randomized controlled studies (varying quality)
- 1 Before-and-after study

NO

- Early versus late epidural studies
Does Epidural Labor Analgesia Cause Intrapartum Fever?

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VOTE

Early versus late epidural studies
Does Epidural Labor Analgesia Cause Intrapartum Fever?

- Many Observational Studies
- 5 Randomized controlled studies (varying quality)
- 1 Before-and-after study

Early versus late epidural studies

Result: No
Does Epidural Labor Analgesia Cause Intrapartum Fever?

- **NO**
  - Early versus late epidural studies

The weight of the evidence is currently supporting the association

- **YES**
  - *Many* Observational Studies
  - 5 Randomized controlled studies (varying quality)
  - 1 Before-and-after study
What are the consequences of epidural fever?
Maternal consequences

If a woman develops a fever:

- Increased likelihood of intrapartum antibiotics
- Increased likelihood of cesarean or assisted vaginal delivery

Fetal consequences

• Less worrisome

• Increased likelihood of a neonatal sepsis evaluation and antibiotic treatment \(^1\)

• May be related to an institution’s neonatal practice style \(^2\)

Fetal consequences

• More worrisome
  • Fetal Hyperthermia associations:
    • Low fetal tone
    • Lower APGAR Scores
    • Bag mask ventilation
    • Tracheal intubation
    • Supplemental oxygen in nursery
    • Cardiopulmonary resuscitation
    • Neonatal seizures
Fetal consequences

- Retrospective cohort
- Low risk, term, nulliparous, singleton pregnancies (n= 3894)
- $T_{\text{max}} > 100.4^\circ F$:
  - Epidural group: 19.2% (535/2784)
  - No epidural group: 2.4% (10/425)
- In patients < 99.5$^\circ F$: No difference between groups
- In patients with epidural analgesia and > 100.4$^\circ F$
  - Linear trend between $T_{\text{max}}$ and all neonatal outcomes examined.

FIGURE 1
Occurrence of neonatal outcomes according to maximum intrapartum temperature among women who used epidural analgesia.

What is the mechanism?

- High ambient temperatures
- Decreased heat-dissipating hyperventilation
- Increased heat-producing shivering
- Altered thermoregulation
- Elevated sweating threshold below block
- Antipyretic effects of IV opioids*
- Noninfectious inflammatory response via proinflammatory cytokines

*Negishi et al. Anesthesiology 2001; 94: 218-222
Best proposed mechanism

An exaggerated noninfectious inflammatory response via proinflammatory cytokines in women laboring with an epidural.

Gonen et al. Am J Perinatol 2000; 17; 127-130
Best proposed mechanism

An exaggerated noninfectious inflammatory response via proinflammatory cytokines in women laboring with an epidural.


Among women who had epidural, elevated IL-6 levels at admission were associated with increase incidence of fever, $p = 0.008$

*Is there a subset of women primed for an intra-partum fever, and does an epidural simply unveil it?*
This theory is not good for babies:

• Intrauterine inflammation → fetal brain inflammation & neurotoxicity in mice

• Even subclinical placental inflammation causes fetal brain injury in animals

• In humans, the link of intra-partum infection and cerebral palsy is well established
  • What’s the contribution of inflammation?
  • Hyperthermia?

Treatment

Active cooling unsuccessful

Prophylactic antibiotics unsuccessful

Anti-inflammatories

• Tylenol unsuccessful

• Pilot epidural dexamethasone study decreased IL-6 levels but not reduce fever

• High-dose steroids works!


Anti-inflammatories

- At time of epidural placement randomized to:
  - Placebo (n=100)
    - Fever in 21.8% (22/100)
  - 25mg IV methylprednisolone q 8hrs (n=50)
    - Fever in 34% (17/50)
  - 100mg IV methylprednisolone q 4hrs(n=49)
    - Fever in 2.0% (1/49)

- High-dose steroids decreased incidence of epidural fever by 90%!  
  \( (p<0.001) \)

Anti-inflammatory drugs
The rest of the story:

- Placebo (n=100)
  - Neonatal bacteremia 0% (0/100)

- 25mg IV methylprednisolone q 8hrs (n=50)
  - Neonatal bacteremia 2.1% (1/50)

- 100mg IV methylprednisolone q 4hrs (n=49)
  - Neonatal bacteremia 9.3% (4/49)

Asymptomatic bacteremia kills babies.

Next Questions

• Does epidural have pro-inflammatory effects?
• Does effective pain relief block a naturally-occurring anti-inflammatory process?
• Can we reproduce this without harm?
• Is there a group of women (with greater admission IL-6 levels) primed for epidural fever?
• Identify ~20% to counsel them against epidural?
• Least pyrogenic labor epidural cocktail?
• Does pro-active labor management?
Embrace the possibility that this phenomenon is real, and move good quality research forward …

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