Fetal Neurodevelopment after Maternal Anesthesia

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Disclosure

No relevant financial relationships with commercial entities
Anesthetic Neurotoxicity

Why should we be concerned?
Anesthetic Neurotoxicity

Why should we be concerned?

Rodents

Neurodegeneration with anesthesia
Learning and behavioral deficits

Jevtovic-Todorovic V et.al, J Neurosci 2003
Anesthetic Neurotoxicity

Why should we be concerned?

**Rodents**

- Neurodegeneration with anesthesia
- Learning and behavioral deficits

Jevtovic-Todorovic V et.al, J Neurosci 2003

**Primates**

- Neurodegeneration in a non-human primate model
- Short duration of anesthetic exposure

Brambrink A et.al, Anesthesiology 2010
Anesthetic Neurotoxicity

Public health importance

Epidemiological association

≥ 2 anesthesia exposures

> 2 hrs of cumulative anesthesia exposure

2-fold increase in the incidence of LD and ADD

Wilder et. al, Anesthesiology 2009
Anesthetic Neurotoxicity

Mechanisms of neurotoxicity

Increased neuronal death during synaptogenesis
Decreased neural stem cell pool
Alteration of dendritic spines
Alteration of cytoskeletal structure of glial cells

*Patel P et. al, Anesthesiology 2009
Anesthetic Neurotoxicity

Mechanisms of neurotoxicity

- Neuronal death
- Neurotoxicity

Mechanisms*

- Increased neuronal death during synaptogenesis
- Decreased neural stem cell pool
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*Patel P et. al, Anesthesiology 2009
Anesthetic Neurotoxicity

Mechanisms of neurotoxicity

- Neuronal death
- Decreased neurogenesis
- Neurotoxicity
- Increased neuronal death during synaptogenesis
- Decreased neural stem cell pool
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*Patel P et. al, Anesthesiology 2009*
Anesthetic Neurotoxicity

Mechanisms of neurotoxicity

- Neuronal death
- Decreased neurogenesis
- Altered spines
- Alteration of cytoskeletal structure of glial cells

Mechanisms*

- Increased neuronal death during synaptogenesis
- Decreased neural stem cell pool
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*Patel P et. al, Anesthesiology 2009
Increased neuronal death during synaptogenesis
Decreased neural stem cell pool
Alteration of dendritic spines
Alteration of cytoskeletal structure of glial cells

Mechanisms*

*Patel P et. al, Anesthesiology 2009
## Anesthetic Neurotoxicity

What we know so far

<table>
<thead>
<tr>
<th>Stage of Vulnerability</th>
<th>Combination of Anesthetics</th>
<th>Duration of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synaptogenesis</td>
<td>Combination of drugs is more neurotoxic</td>
<td>Prolonged duration</td>
</tr>
<tr>
<td>Neurogenesis</td>
<td>Different mechanisms of action</td>
<td>Repeated or cumulative exposure</td>
</tr>
<tr>
<td>Neuronal migration?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Big Question

Is the fetal brain really vulnerable to the adverse effects of anesthetic agents?
Anesthetic Neurotoxicity

Stages of neurodevelopment

- Neurogenesis
- Migration
- Differentiation
- Synaptogenesis
- Remodeling
Anesthetic Neurotoxicity

Stages of neurodevelopment

- Neurogenesis
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Anesthetic Neurotoxicity

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Anesthetic Neurotoxicity

Stages of neurodevelopment

- Neurogenesis
- Migration
- Differentiation
- Synaptogenesis
- Remodeling

Birth

GABA

Glutamate
Fetal Neurodevelopment

GABA is excitatory

Ben-Ari Y, Nat Rev Neurosci 2002
Fetal Neurodevelopment

GABA is excitatory

Ben-Ari Y, Nat Rev Neurosci 2002
Fetal Neurodevelopment

GABA is **excitatory**

Ben-Ari Y, Nat Rev Neurosci 2002
Fetal Neurodevelopment

GABA is excitatory

Ben-Ari Y, Nat Rev Neurosci 2002
Fetal Neurodevelopment

GABA is excitatory

Ben-Ari Y, Nat Rev Neurosci 2002
Wang DD et al, J Physiol 2009
Wang DD et. al, J Physiol 2009
Wang DD et al, J Physiol 2009
Fetal Neurodevelopment

Presence of maternal hormones
Fetal Neurodevelopment

Presence of maternal hormones

Progesterone

Neural stem cell proliferation

Interaction with GABA_A
Fetal Neurodevelopment

Presence of maternal hormones

**Progesterone**
- Neural stem cell proliferation
- Interaction with GABA<sub>A</sub>

**Estradiol**
- Modulation of apoptosis
- Subcellular signaling mechanisms
- Dendritic growth
Fetal Neurodevelopment
Presence of maternal hormones

**Progesterone**
- Neural stem cell proliferation
- Interaction with GABA_A

**Estradiol**
- Modulation of apoptosis
- Subcellular signaling mechanisms
- Dendritic growth

**Oxytocin**
- Transient GABA-ergic signaling
- Depolarizing to hyperpolarizing switch
Fetal Neurodevelopment

GABA is evolutionarily conserved
Fetal Neurodevelopment

GABA is evolutionarily conserved

Pollen
Fetal Neurodevelopment

GABA is evolutionarily conserved

Pollen

Tomato
Fetal Neurodevelopment

GABA is evolutionarily conserved

Pollen

Tomato

Beetle
Fetal Neurodevelopment

GABA is evolutionarily conserved

- Pollen
- Beetle
- Tomato
- Drosophila
Fetal Neurodevelopment

A tale of two trimesters
Fetal Neurodevelopment
A tale of two trimesters

First trimester
Teratogenic effects
Fetal Neurodevelopment

A tale of two trimesters

First trimester

Teratogenic effects

Third trimester

Effects on the newborn
Fetal Neurodevelopment

A tale of two trimesters

- First trimester
  - Teratogenic effects

- Second trimester
  - Unknown?

- Third trimester
  - Effects on the newborn
Third trimester
Third Trimester
Developmental neurotoxicity of anesthetic agents

**Question**

Does a single exposure to 1 MAC isoflurane during third trimester impact fetal brain development?

**Findings**

No histological changes
No behavioral changes

Li Y et. al, Neuropharmacology 2007
Third Trimester
Developmental neurotoxicity of anesthetic agents

Wang S et.al, Pediatr Res 2009
Third Trimester
Evidence from human studies

Study methodology

Population-based birth cohort, 1976-82
N = 5320

Vaginal = 4823
CD = 497 (GA = 193, RA = 304)

Sprung J et. al, Anesthesiology 2009
Third Trimester

Evidence from human studies

Sprung J et. al, Anesthesiology 2009
Third Trimester

Evidence from human studies

Sprung J et. al, Anesthesiology 2009
Is second trimester vulnerable?
Second Trimester
Evidence from a rodent model
## Second Trimester

Evidence from a rodent model

<table>
<thead>
<tr>
<th>E 14</th>
<th>2nd trimester</th>
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<tbody>
<tr>
<td><img src="#" alt="Control 100% oxygen" /> 4h</td>
<td><img src="#" alt="Isoflurane 1.4%" /> 4h</td>
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*Note: Images represent experimental conditions.*
## Second Trimester

### Evidence from a rodent model

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- **Control 100% oxygen 4h**
- **Isoflurane 1.4% 4h**

### Monitoring

- Hemodynamics, metabolic, respiratory stability
Second Trimester
Evidence from a rodent model

E 14
2nd trimester

Control 100% oxygen 4h
Isoflurane 1.4% 4h

Hemodynamics, metabolic, respiratory stability

Delivery E 22 (term)
Second Trimester
Evidence from a rodent model

E 14
2nd trimester

Control 100% oxygen 4h
Isoflurane 1.4% 4h

Monitoring
Hemodynamics, metabolic, respiratory stability

Delivery
Delivery E 22 (term)

PND 60 Adulthood
Behavioral testing
Second Trimester
Evidence from a rodent model

Palanisamy A et. al, Anesthesiology 2011
Second Trimester
Impaired spatial memory after in utero isoflurane exposure

Palanisamy A et al., Anesthesiology 2011
Big Question

What are the possible mechanisms behind these behavioral abnormalities?
Second Trimester
Isoflurane inhibits neurogenesis in a cell culture model

Sall J et al, Anesthesiology 2009
Second Trimester
Isoflurane inhibits neurogenesis in a cell culture model

![Graph showing fold increase in median IQR](Image)

Sall J et al, Anesthesiology 2009
Second Trimester
Isoflurane inhibits neurogenesis in a cell culture model

Sall J et al, Anesthesiology 2009
Second Trimester
Isoflurane inhibits neurogenesis in a cell culture model

Sall J et al, Anesthesiology 2009
Second Trimester

Isoflurane inhibits neurogenesis in a cell culture model

Culley DJ et al, Anesthesiology 2011
Second Trimester
Sevoflurane induces brain inflammation in utero

Question
Does in utero exposure to sevoflurane induce inflammation in the fetal brain?

Model
Pregnant mouse E 14
2.5% sevoflurane for 2 h

Zheng H et al, Anesthesiology 2013
Second Trimester

Sevoflurane induces brain inflammation in utero

B

IL-6 levels (%)  

Control  Sevoflurane

D

PSD-95 levels (%)  

Control  Sevoflurane

B

Synaptophysin levels (%)  

Control  Sevoflurane

F

Caspase-3 activation (%)  

Control  Sevoflurane

P = 0.026

P = 0.036

P = 0.0003

P = 0.0075

*  

**
Second Trimester

Neurotoxic effects of ketamine

Primate study

Pregnant macaques at G120 (2nd trimester)
Neonatal macaques at P6
IV ketamine infusion (dose range)

Primary outcome measure

Neuroapoptosis in brain regions

Brambrink AM et. al, Anesthesiology 2012; 116:372-84
Second Trimester

Neurotoxic effects of ketamine

FETAL APOPTOSIS PATTERN
Second Trimester

Neurotoxic effects of ketamine

FETAL APOPTOSIS PATTERN
Second Trimester

Neurotoxic effects

Mean number of apoptotic neurons per brain ($\times 10^6$)

- Control Fetal
- Keta Fetal
- Control Neonatal
- Keta Neonatal
Second Trimester

Neurotoxic effects

Mean number of apoptotic neurons per brain ($\times 10^6$)

- Control (FETAL)
- Keta (FETAL)
- Control (NEONATAL)
- Keta (NEONATAL)
Second Trimester

Neurotoxic effects

Mean number of apoptotic neurons per brain ($\times 10^6$)
Second Trimester

Neurotoxic effects

- Mean number of apoptotic neurons per brain ($\times 10^6$)
- Control vs. Keta comparison for Fetal and Neonatal stages
- 2-fold increase in neurotoxic effects
Second Trimester

Neurotoxic effects of propofol

Primate study

Pregnant macaques at G120 (2nd trimester)

Neonatal macaques at P6

IV propofol infusion 5 h (dose range)

Primary outcome measure

Neuroapoptosis in brain regions at 3 h

Creeley C et. al, Br J Anaesth; 110: i29-i38
Second Trimester

Neurotoxic effects of propofol

2.4-fold

3.8-fold

Creeley C et. al, Br J Anaesth; 110: i29-i38
Second Trimester
Neurotoxic effects of isoflurane

Primate study
Pregnant macaques at G120 (2nd trimester)
Neonatal macaques at P6
Isoflurane titrated for 5 h

Primary outcome measure
Neuroapoptosis in brain regions at 3 h after cessation of anesthesia

Creeley C et. al, Anesthesiology 2013; 116:372-84
Second Trimester

Neurotoxic effects of isoflurane

Creeley C et al, Anesthesiology 2013; 116:372-84
Non-human primate brain is susceptible to the effects of even a short duration of anesthesia.

Effects occur with all classes of anesthetic agents.

Fetal brain is differentially susceptible.

Both neurons and oligodendrocytes are affected.
Inhibition of Neurogenesis
Decreased proliferation of neural stem cells
Inhibition of Neurogenesis
Decreased proliferation of neural stem cells

Permanent Alteration of Synaptic Mechanisms
Changes in synaptic proteins, decreased PSD-95
<table>
<thead>
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<th>Induction of Inflammation</th>
<th>3</th>
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<td>Fetal brain inflammation, increased IL-6</td>
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<td>Inhibition of Neurogenesis</td>
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<tr>
<th>Neuronal and Oligo-apoptosis</th>
<th>4</th>
</tr>
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<tr>
<td>Degeneration of neurons and oligodendrocytes</td>
<td></td>
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</tbody>
</table>
Big Question

Is propofol a viable alternative?
Use of Propofol?

Not enough evidence

Safety profile unclear
Neurodegeneration in NHP model
Alters dendritic spines
Behavioral studies needed
Caveats

Difficulty with extrapolation of animal studies
Caveats

Difficulty with extrapolation of animal studies
Caveats

Difficulty with extrapolation of animal studies
Caveats
Translating neurodevelopmental time

TR ANSLATING T IME
across developing mammalian brains

1. Species One
   - Hamster
   - Mouse
   - Rat
   - Rabbit
   - Spiny mouse
   - Guinea pig
   - Ferret
   - Cat
   - Macaque
   - Human

2. Days Post Conception (Species one)
   - 10.5 < 14 < 35

3. Species Two
   - Hamster
   - Mouse
   - Rat
   - Rabbit
   - Spiny mouse
   - Guinea pig
   - Ferret
   - Cat
   - Macaque
   - Human

Results
14 PC days in Rat neurodevelopment equates to Human neurodevelopment as follows:
   - Cortical Events: 65.3 PC days
   - Limbic Events: 48.3 PC days
   - Non-cortical/limbic Events: 51.9 PC days

GO BACK
*Why do primates have 3 predictions? The Model*
Caveats
Longer relative duration of exposure

Rodent
Duration of gestation
22 days

4 h in rat

48 h in humans

Human
Duration of gestation
280 days
### Caveats

**Human neural development**

<table>
<thead>
<tr>
<th></th>
<th>Rodents</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurons</td>
<td>70-200 million</td>
<td>86000 billion</td>
</tr>
<tr>
<td>Cerebral cortex size</td>
<td>42%</td>
<td>82%</td>
</tr>
<tr>
<td>Neurogenesis cycle</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Migration distance</td>
<td>Shorter</td>
<td>Longer</td>
</tr>
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</table>
## What Will You Tell The Mother?

**Summary**

<table>
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<tr>
<th>Teratogenic effects</th>
<th>No evidence for teratogenicity with a single clinically relevant exposure</th>
</tr>
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<tr>
<td>Lack of human data</td>
<td>For second trimester exposures despite emerging animal evidence</td>
</tr>
<tr>
<td>No adverse effects</td>
<td>During the third trimester</td>
</tr>
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