Autism and Induction of Labor: Talking Points for the Obstetrician

Erin A. S. Clark
Maternal Fetal Medicine
Your clinic: G1, 38 weeks

- You:
  “Your blood pressure is high, and it is time to have a baby. We need to induce your labor.”

- Your patient:
  “OK…but I don’t want pitocin.”
You:

“Pitocin is how we induce your labor.”

Your patient:

“I don’t want any pitocin.
I don’t want my kid to have autism.”
Your clinic: G1, 38 weeks

- **You:**
  
  ...try to conjour a brief, compelling, evidence-based answer....

And say, “*Pitocin doesn’t cause autism.*”
Your clinic: G1, 38 weeks

- You, after further thought:
  “Your preeclampsia is a lot more serious than a theoretic risk of autism.”

- Your patient:
  “I don’t want any pitocin.”
Objectives

- What is autism?
- How often does it occur?
- What causes it?
- What doesn’t cause it?
Induced Labor Linked to Raised Risk of Autism, Study Suggests

Male children seem to be most vulnerable, researchers report.

Study Links Inducing/Augmenting Labor Modestly Higher Autism Risk

Inducing Labor Could Hurt Your Baby More Than You Know

Natural birth advocates often anger some over their stance on really trying to have a non-mediated birth without induction unless it's absolutely necessary. There will...
North Carolina Epidemiologic Study

- Largest epidemiologic study to date
- Published August 2013, JAMA Pediatrics
What is autism spectrum disorder?

- A ‘spectrum’ of developmental disabilities
  - Autism disorder
  - Asperger disorder
  - Pervasive developmental disorder, NOS

- 40% have intellectual disability (IQ <70)
What is the age at diagnosis?

- Age 2-3: Earliest possible diagnosis
- Age 4: Average age at diagnosis
- Age 8: Clinical gold standard
  - CDC ascertainment
How is it diagnosed?

- There is no single medical test
- Requires a detailed exam by a qualified professional
  - Comprehensive psychologic & behavioral eval
  - Clinical and parental observation
  - Speech and language assessment
Autism Prevalence: U.S.

1 in 68

CDC ADDM Network, 2010
Autism Prevalence: UTAH

1 in 54

CDC ADDM Network, 2010
Autism Prevalence

\[
\frac{\text{Number of 8-year-olds with ASDs}}{\text{Total number of 8-year-olds}} = \text{PREVALENCE}
\]
Autism Prevalence

Increased 120%
between 2002-2010

CDC ADDM Network, 2010
Explanation is multi-factorial

- Changes in case ascertainment
- Legitimate increase in prevalence?
Autism Prevalence

- Boys affected 4-5 x as often as girls
  - Consistent epidemiologic finding
  - Reasons are unclear
    - Diagnostic bias
    - Female protective effect
  - Need to stratify analyses by sex
A child with ASD might:

- Not respond by name by 12 mo.
- Not point at objects with interest by 14 mo.
- Not play “pretend” by 18 mo.
- Avoid eye contact and prefer to be alone
- Have trouble understanding feelings
- Have delayed speech and language
A child with ASD might:

- Repeat words and phrases over and over
- Get upset by minor changes in routine
- Have obsessive interests
- Do hand-flapping, spinning in circles, rocking
- Have unusual reactions to the way things look, sound, taste, or feel
What doesn’t cause it?

- Vaccinations (MMR)
  - Immune system compromise / autoimmune rxn
  - Mercury-based preservatives (thimerosal)
  - Soundly refuted by medical research
    - >20 peer-reviewed negative epidemiologic studies
    - Dr. Wakefield’s original 1998 study discredited (falsified data)
What causes it?

Genetic Risk
+
Environmental Risk
## Prenatal Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male fetus</td>
<td>4 - 5</td>
</tr>
<tr>
<td>Advanced maternal age (&gt;35)</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Advanced paternal age (&gt;35)</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>Parity (first vs. ≥3)</td>
<td>1.6 (1.4-1.8)</td>
</tr>
<tr>
<td>Antepartum bleeding</td>
<td>1.8 (1.1-2.9)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.7 (1.3-2.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.1 (1.2-3.5)</td>
</tr>
</tbody>
</table>

# Perinatal Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>&lt;37 weeks</td>
<td>2.2 (1.5-3.5)</td>
</tr>
<tr>
<td>&lt;28 weeks</td>
<td>2.8 (1.6-3.9)</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>2.1 (1.1-4.0)</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td></td>
</tr>
<tr>
<td>All indications</td>
<td>1.6 (1.1-2.3)</td>
</tr>
<tr>
<td>Scheduled</td>
<td>1.8 (1.3-2.5)</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>1.5 (1.1-2.1)</td>
</tr>
</tbody>
</table>

## Neonatal Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjusted Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational age</td>
<td>2.1 (1.1-3.9)</td>
</tr>
<tr>
<td>Low 5 minute Apgar</td>
<td>3.2 (1.2-8.2)</td>
</tr>
<tr>
<td>NICU transfer</td>
<td>1.8 (1.3-2.7)</td>
</tr>
<tr>
<td>Neonatal encephalopathy</td>
<td>5.6 (2.3-13.5)</td>
</tr>
<tr>
<td>Birth defects</td>
<td>1.9 (1.1-3.5)</td>
</tr>
</tbody>
</table>

Oxytocin and ASD

- Role for endogenous oxytocin in normal human social and behavioral development
- Functional oxytocin deficiency and a faulty oxytocin signaling pathway have been observed in some studies of ASD
- *Does synthetic oxytocin used for labor induction alter fetal oxytocin receptors and predispose offspring to ASD?*
Induction of Labor and ASD

Leading up to 2013...

- 3 studies that showed weak association
  - Of these, only 1 showed a persistent association after controlling for confounders
- 6 studies that didn’t
- All limited by small size and methodology

North Carolina Epidemiologic Study

- Largest epidemiologic study to date
- Published August 2013, JAMA Pediatrics
Association with ASD

- Induced / augmented: OR 1.27 (1.01-1.52)
- Induced only: OR 1.13 (1.04-1.22)
- Augmented only: OR 1.16 (1.07-1.25)
Association with ASD: **MALES**

- Induced / augmented: OR 1.35 (1.1-1.66)
- Induced only: OR 1.18 (1.08-1.3)
- Augmented only: OR 1.15 (1.05-1.25)
North Carolina Epidemiologic Study

- Association with ASD: FEMALES
  - Induced / augmented: OR 1.01 (0.67-1.53)
  - Induced only: OR 0.95 (0.8-1.13)
  - Augmented only: OR 1.18 (1.02-1.36)
Highly criticized:

- Exposure data came from birth certificates (Induction/augmentation agent was not known)
- Limited ability to control for confounders
Con founding in Autism Research

- AMA ↗ autism
- AMA ↗ induction of labor

- If you don’t account for maternal age in analyses, it may look like induction of labor is associated with autism
Confoundning in Autism Research

AMA

Induction  Autism
Response from SMFM / ACOG

- **SMFM Statement, 2014**
  “Labor Induction or Augmentation and Autism Spectrum Disorders”

- **ACOG Committee Opinion #597, May 2014**
  “Labor Induction or Augmentation and Autism”
“...current evidence does not identify a causal relationship between labor induction or augmentation in general, or oxytocin labor induction specifically, and autism or ASD.”
“Recognizing the limitations of available study design, conflicting data, and the potential consequences of limiting labor induction and augmentation, the Committee on Obstetric Practice recommends against a change in current guidance regarding counseling and indications for and methods of labor induction and augmentation.”
Utah Data – SMFM 2015

- Epidemiologic analysis using
  - Utah Registry of Autism and Developmental Disabilities (URADD)
  - Utah Department of Education
  - Utah Department of Health Vital Statistics

- 2,266 ASD cases
- 151,845 controls
Controlled for socioeconomic status, maternal health, pregnancy-related events and conditions, and birth year.

### Table. Association between labor induction and/or augmentation and autism spectrum disorder in a Utah cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction/augmentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not induced and not augmented</td>
<td>1 [REFERENCE]</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Induced and augmented</td>
<td>0.887</td>
<td>0.740-1.063</td>
<td>0.19</td>
</tr>
<tr>
<td>Induced only</td>
<td>0.973</td>
<td>0.875-1.083</td>
<td>0.62</td>
</tr>
<tr>
<td>Augmented only</td>
<td>0.980</td>
<td>0.869-1.105</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Entire sample<sup>b</sup>

(n<sub>cases</sub> = 2266, n<sub>controls</sub> = 151,845)
Induction and/or augmentation during childbirth are not associated with increased odds of ASD in childhood in a large Utah cohort.

Results were not different for males vs. females.
Summary

- U.S. incidence of autism is now 1 in 68
- Environmental and genetic risk factors both contribute to risk
- Perinatal risk factors have been identified
- Best available research shows no link between autism & induction/augmentation
  - Careful discussions of induction risk/benefit needed
Your clinic: G₁, 38 weeks

- The best available research shows no link between induction of labor and autism.

- We should not avoid induction of labor, or Pitocin, when it is medically indicated.

- To do so may increase your risk of cesarean, and could put you and your baby at increased risk.