Title: Rates and clinical implication of transplacental transfer of neuraxial fentanyl to neonates

Authors: Katrina Mark, MD\textsuperscript{2}, Olivia LeBeau MD\textsuperscript{1}, Miranda Gibbons\textsuperscript{2}, Peter Rock MD\textsuperscript{2}, Bhavani Kodali MD\textsuperscript{2}, Megan G Anders MD, MS\textsuperscript{2}, Katherine Goetzinger MD\textsuperscript{2}

1. INOVA Fairfax Hospital, Falls Church VA
2. University of Maryland School of Medicine, Baltimore MD

Corresponding author:
Katrina Mark, MD FACOG
Associate Professor
University of Maryland School of Medicine
11 S Paca Street, Suite 400
Email: kmark@som.umaryland.edu
Phone: 410-328-5964
Fax: 410-328-3589

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Objective: Although epidural analgesia is widely accepted as a safe practice, concerns have been raised regarding the possibility of physiologic effects on the neonate resulting from the transplacental transfer of epidurally administered opioids.\textsuperscript{1-3} The objectives of this study were to determine the frequency of fentanyl positivity on neonatal urine drug testing as a result of transplacental transfer from neuraxial analgesia, the factors that increase the likelihood of fentanyl positivity, and whether fentanyl positivity is associated with any clinically significant outcomes in the immediate neonatal period.

Study Design: This is a retrospective cohort study of all deliveries involving neuraxial analgesia with fentanyl at an academic medical center between 2018 and 2020 where universal neonatal urine toxicology testing for fentanyl is performed. Those that did not receive neuraxial fentanyl, had a positive maternal fentanyl test prior to epidural administration, had maternal or neonatal intravenous fentanyl administered, or delivered an infant less than 24 weeks of gestation were excluded. Immediate birth outcomes and maternal characteristics were compared between infants who tested positive and those who tested negative for fentanyl. Stratified analyses were conducted to address the potential confounding effects of gestational age at delivery and delivery method on immediate neonatal outcome. This study was approved by the IRB at the University of Maryland.

Results: During the study period, 3,594 births occurred and 2,272 maternal/infant pairs were included in analysis. Urine toxicology testing was positive for fentanyl in 48% of infants. The mothers of the neonates who tested positive were more likely to be primiparous (66.7% vs 33.2%, \( p < 0.001 \)), had epidurals for a longer period of time (11.2 vs 1.8 hours, \( p < 0.001 \)) and received a higher dose of neuraxial fentanyl (433.4mcg vs 73.0mcg, \( p < 0.001 \)).

After adjusting for associated factors, infants born by vaginal delivery and unscheduled cesarean section had a 29.5 and 84.8 times higher odds of testing positive for fentanyl, respectively, when compared to those delivered by scheduled cesarean section. There was a
dose-dependent relationship between amount of fentanyl administered and likelihood of positive infant toxicology testing; for example, 0.9% of infants whose birth parent received 10mcg of neuraxial fentanyl tested positive and 90.2% of those receiving more than 200mcg of fentanyl tested positive (Supplemental Figure 1).

To evaluate birth outcomes, analysis was restricted to term neonates (≥37 weeks gestation) (N = 1,767). Neonates that tested positive for fentanyl were more likely to have a 5 minute Apgar score less than 7 (2.8% vs 0.9%, aOR 4.8 [1.9-11.9]), but otherwise had similar birth outcomes (Table 1). Need for resuscitation and NICU admission were higher in the fentanyl negative group, but after adjusting for gestational age at birth by week and mode of delivery, these findings were no longer significant.

Conclusions: Transplacental transfer of fentanyl and subsequent positive neonatal urine toxicology testing occurs in almost half of deliveries involving fentanyl-containing neuraxial analgesia. The likelihood of this transfer increases in a dose-dependent manner. There does not appear to be any immediate clinically significant consequences associated with neonatal fentanyl positivity.
References:


Table 1: Comparison of immediate birth outcomes of term neonates that test positive and negative for fentanyl

<table>
<thead>
<tr>
<th></th>
<th>Baby Fentanyl positive</th>
<th>Baby Fentanyl negative</th>
<th>OR (95% CI)</th>
<th>aOR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 minute APGAR score &lt;7</td>
<td>2.8%</td>
<td>0.9%</td>
<td>2.9 (1.3-6.8)</td>
<td>4.8* (1.9-11.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Need for resuscitation</td>
<td>15.4%</td>
<td>22.4%</td>
<td>0.7 (0.6-0.8)</td>
<td>1.3* (0.9-1.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>NICU admission</td>
<td>12.2%</td>
<td>21.3%</td>
<td>0.6 (0.5-0.7)</td>
<td>0.9* (0.6-1.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Cesarean Delivery</td>
<td>16.3%</td>
<td>59.9%</td>
<td>0.3 (0.2-0.4)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>39.4 +/- 1.1</td>
<td>38.8 +/- 1.0</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birthweight</td>
<td>3259 +/- 437</td>
<td>3193 +/- 519</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Dose of epidural</td>
<td>430 +/- 297</td>
<td>75 +/- 105</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of Epidural before delivery (hours)</td>
<td>11 +/-8</td>
<td>2 +/- 2</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusting for mode of delivery, gestational age

#Adjusting for mode of delivery