Pain Management in Pregnancy and Delivery

Friday, October 28, 2022 12-1pm EST

Broadcast via GoMeeting

Presented by:

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MotherToBaby

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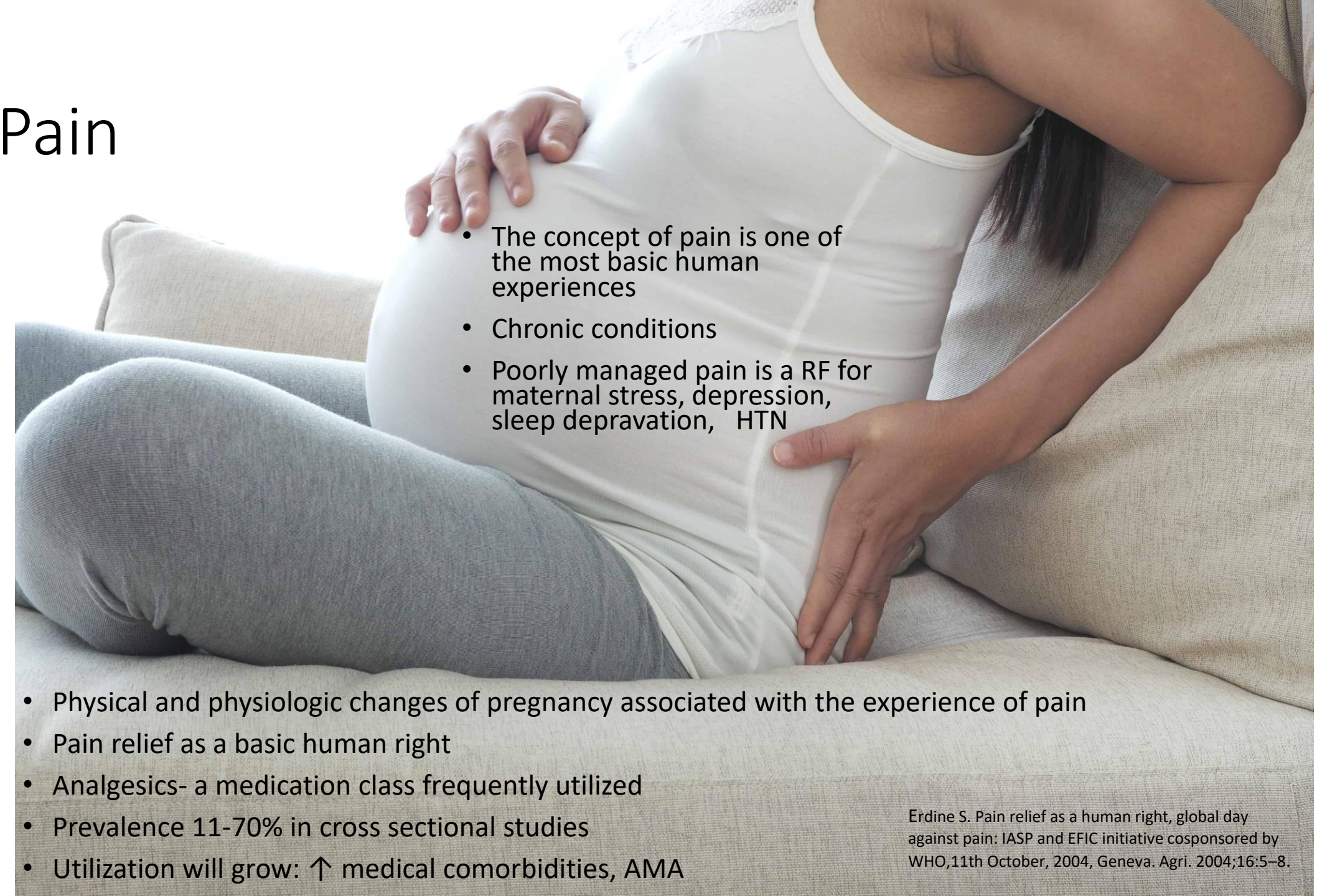
Organization of Teratology Information Specialists

Pain



- The concept of pain is one of the most basic human experiences
- Chronic conditions
- Poorly managed pain is a RF for maternal stress, depression, sleep depravation, HTN

- Physical and physiologic changes of pregnancy associated with the experience of pain
- Pain relief as a basic human right
- Analgesics- a medication class frequently utilized
- Prevalence 11-70% in cross sectional studies
- Utilization will grow: ↑ medical comorbidities, AMA

Erdine S. Pain relief as a human right, global day against pain: IASP and EFIC initiative cosponsored by WHO,11th October, 2004, Geneva. Agri. 2004;16:5–8.

Pain management

- We recognize that there are a variety of way to heal pain
- Acupuncture, local anesthetics, antidepressants, antiepileptic drugs, therapy

- For the purposes of our talk, we will review:
  - The role, uses, risks of NSAIDS
  - The use of acetaminophen
  - The use of aspirin
  - Labor pain management
  - Use of opioids and neonatal abstinence syndrome

Non-steroidal Anti-inflammatory drugs

NSAIDS

- Analgesic and anti-inflammatory actions mediated by inhibition of prostaglandin synthesis/ COX enzymes
- Miscarriage risk- use of NSAIDs around time of conception or longer term use (>1 week)

Table 1. Adjusted Odds Ratios (aORs) for an Association Between Risk for Miscarriage (MC) and Prenatal NSAID Exposure

Author/study type	No. of Women	NSAID Exposure criteria	NSAID *n* (%)	Effect Size: aOR or aHR (95% CI)	
Daniel et al. (2014)[67] Retrospective cohort	65,457	Any type of prescribed NSAID dispensed between 2 weeks pre-conception to week 20 of gestation Exposure based on dispensing of medications	4,495 (6.9%)	Nonselective COX inhibitors, any type	1.10 (0.99 to 1.22)
				Ibuprofen	1.06 (0.93 to 1.22)
				Diclofenac	1.19 (0.97 to 1.46)
				Naproxen	0.97 (0.74 to 1.28)
				Indomethacin	**2.82 (1.70 to 4.69)**
				COX-2 selective inhibitor, any type	1.43 (0.79 to 2.59)
Edwards et al. (2012)[66] Prospective cohort	2,780	Any type of over-the-counter NSAID used between last menstrual period and week 6 of gestation Exposure based on self-reported use	1,185 (43%)	Any NSAID use	1.00 (0.81 to 1.23)
				NSAIDs used for 1 to 2 days	0.91 (0.70 to 1.17)
				NSAIDs used for 3 to 5 days	1.05 (0.75 to 1.46)
				NSAIDs used for 6 to 7 days	1.32 (0.65 to 2.69)
				NSAIDs used for > 7 days	1.11 (0.66 to 1.89)
Li et al. (2003)[29] Prospective cohort	1,055	Any type of over-the-counter or prescribed NSAID used between last menstrual period and date of pregnancy confirmation Exposure based on self-reported use	53 (5%)	NSAID taken during early pregnancy	**1.8 (1.0 to 3.2)**
				NSAID taken near time of conception	**5.6 (2.3 to 13.7)**
				NSAID taken for <1 week	1.3 (0.7 to 2.6)
				NSAID taken for >1 week	**8.1 (2.8 to 23.4)**
Nakhai-Pour et al. (2011)[69] Case control	4,705 cases	Any type of prescribed NSAID use between the start of pregnancy and MC	352 cases (7.5%)	Any NSAID use	**2.43 (2.12 to 2.79)**
	47,050 controls	Exposure based on dispensed NSAID data	1,213 controls (2.6%)	Ibuprofen	**2.19 (1.61 to 2.96)**
				Diclofenac	**3.09 (1.96 to 4.87)**
				Naproxen	**2.64 (2.13 to 3.28)**
				Rofecoxib	**1.83 (1.24 to 2.70)**
				Celecoxib	**2.21 (1.42 to 3.45)**
Nielsen et al. (2001)[68] Case control	4,268 cases	Any type of prescribed NSAID use in the 12 weeks prior to the MC	126 cases (2.9%)	NSAID taken:	
	29,750 controls	Exposure based on data from prescription registry	636 controls (2.1%)	Within 1 week of MC	**6.99 (2.75 to 17.74)**
				2 to 3 weeks prior to MC	**3.0 (1.21 to 7.44)**
				4 to 6 weeks prior to MC	**4.38 (2.66 to 7.20)**
				7 to 9 weeks prior to MC	**2.69 (1.81 to 4.00)**
				10 to 12 weeks prior to MC	1.26 (0.85 to 1.87)

NSAIDS and risk of birth defects

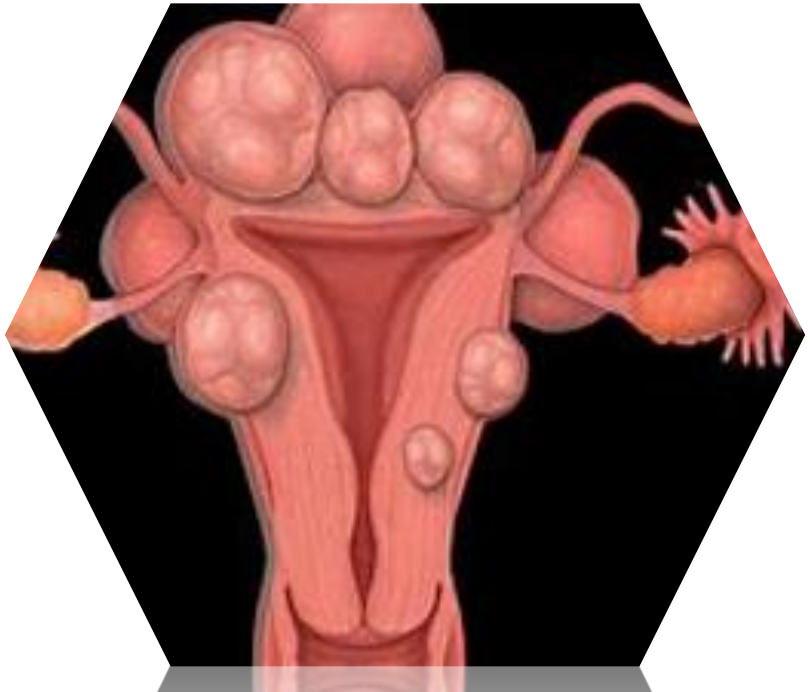
Table 2. Adjusted Odds Ratios (aORs) for an Association Between Risk for Congenital Malformation and Prenatal NSAID Exposure

Author/Year/Study Type	No. of Women	Exposure	Malformation Type	Effect size: aOR or aHR (95% CI)	
Daniel et al. (2012)[72] Retrospective cohort	110,783	Exposure based on pharmacy dispensing of any type of NSAID in the first trimester	Any malformation	Ibuprofen	1.06 (0.90 to 1.24)
				Diclofenac	1.08 (0.87 to 1.34)
				Indomethacin	1.76 (0.96 to 3.19)
				Naproxen	1.09 (0.84 to 1.41)
				COX-2 selective inhibitors	1.40 (0.70 to 2.78)
Nezvalová-Henriksen et al. (2013)[27] Prospective cohort	90,417	Self-reported use of any NSAID type throughout all trimesters of pregnancy and in first trimester (results reported are first trimester)	Any malformation	Ibuprofen	1.0 (0.8 to 1.1)
				Diclofenac	0.5 (0.2 to 1.3)
				Piroxicam	1.0 (0.4 to 2.8)
			Structural heart defect	Ibuprofen	**1.2 (1.0 to 1.6)**
				Diclofenac	0.8 (0.2 to 3.5)
				Piroxicam	2.3 (0.5 to 9.3)
Van Gelder et al. (2011)[28] Prospective cohort	67,891	Self-reported use of any NSAID type in first 12 weeks of pregnancy	Any malformation	Any type of NSAID	0.7 (0.4 to 1.1)
			Congenital heart defects	Any type of NSAID	0.9 (0.5 to 1.4)
Nielsen et al. (2001)[68] Retrospective cohort	18,721	Prescription NSAIDs filled at any time throughout pregnancy (registry data)	Any malformation	Any type of NSAID	1.27 (0.93 to 1.75)
Cassina et al. (2010)[73] Prospective cohort	646	Self-reported use of diclofenac between weeks 5 to 14 of gestation	Any malformation	Diclofenac	2.5 (unadjusted) (0.9 to 6.6)
Ericson et al. (2001)[74] Prospective cohort	2,557	Self-reported use of any NSAID type in first trimester	Any malformation	Any type of NSAID	1.04 (0.84 to 1.29)
Werler et al. (2009)[70] Case control	514 cases 3,277 controls	Self-reported use of any NSAID type in first trimester	Gastroschisis	Any type of NSAID	**1.4 (1.1 to 1.7)**
Bateman et al. (2004)[75] Case control	296 cases	Self-reported use of any NSAID type between 3 months prior to LMP (pre-conception) and during first trimester	Ventricular septal defects	Any type of NSAID pre-conception	1.15 (0.6 to 2.21)
	296 controls			Any type of NSAID first trimester	3.29 (0.88 to 12.31)

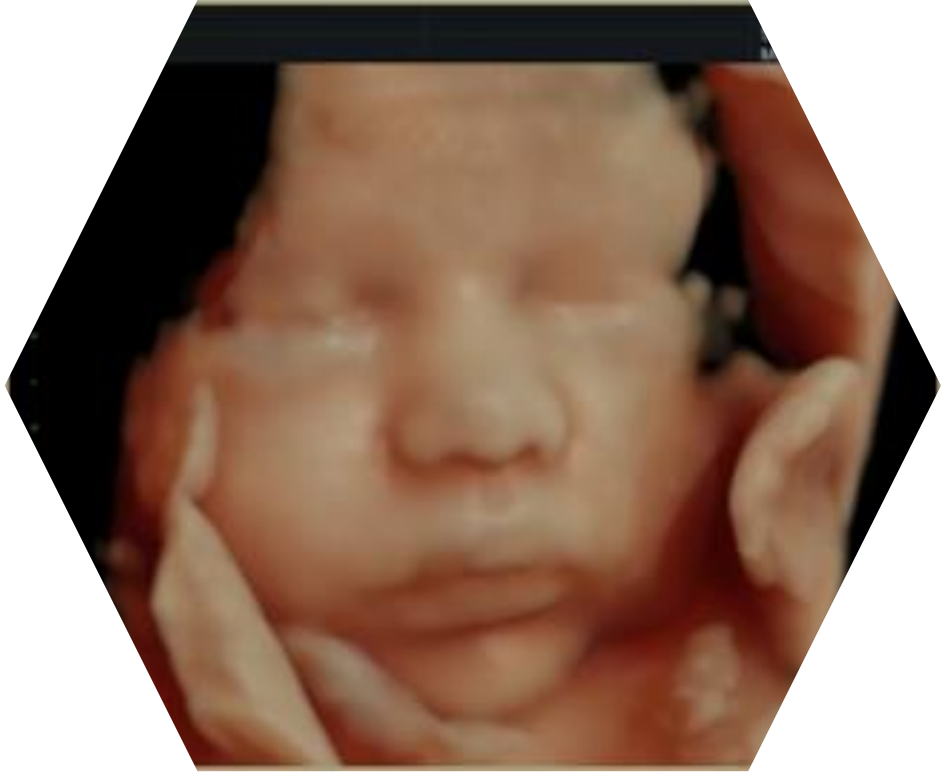
Who in pregnancy would need NSAIDS anyway?

Pregnancy complication- Fibroids

- Fibroids change in size during pregnancy
- Necrosis is painful
- Anti-inflammatory analgesic – indomethacin 25-50 mg PO q 6 hours for 48 hours
- Toradol
- Ibuprofen



NSAIDS and the third trimester



- NSAIDS decrease uterine activity in animal studies
- Used in humans as a tocolytic- though not overtly effective

  -Indocin – risk of delivery, allow steroids to be given for fetal lung maturity (24 hours)

- Closure of the PDA → prematurely
- Decrease in amniotic fluid

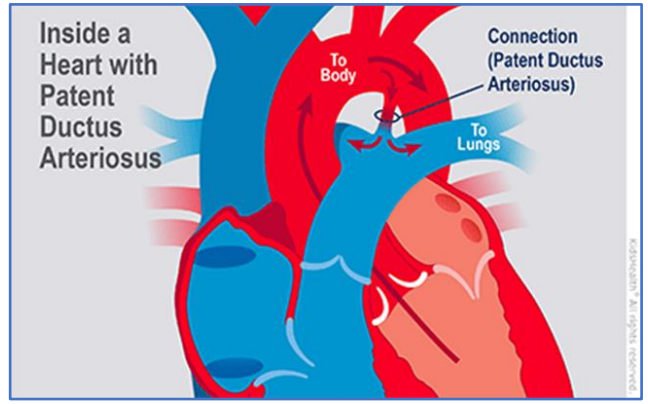
NSAIDS- closure of the PDA

- The ductus arteriosus is a fetal vessel that allows the oxygenated blood from the placenta to bypass the lungs in utero.

- At birth, the lungs fill with air with the first breaths, pulmonary vascular resistance drops, and blood flows from the right ventricle to the lungs for oxygenation.

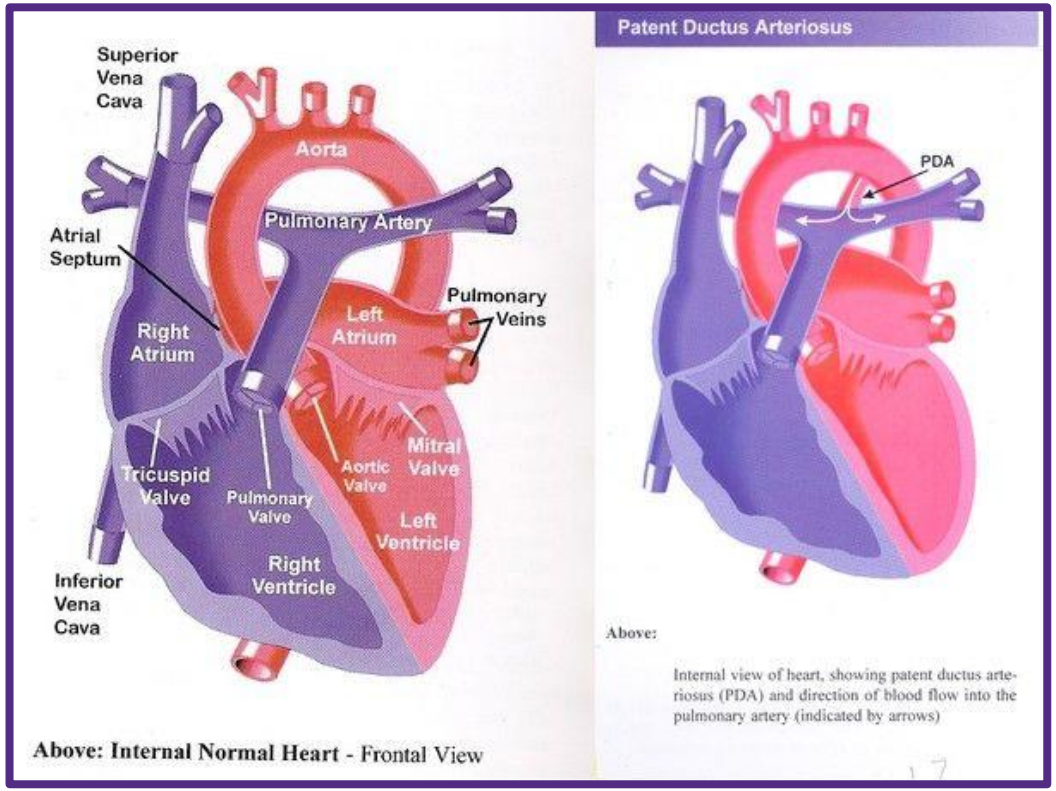
- The increased arterial oxygen tension and decrease in blood flow through the ductus arteriosus → the ductus to constrict and functionally close by 12 - 24 hrs with anatomic closure occurring within 2 to 3 weeks

NSAIDS- closure of the PDA



- The patency is promoted by prostaglandin E 2
- If the ductus remains patent after birth, associated with:
  - pulmonary edema and pulmonary hemorrhage
  - necrotizing enterocolitis
  - intraventricular hemorrhage
  - congestive heart failure
  - renal failure
  - bronchopulmonary dysplasia
- Left to right blood flow causing
- Pulmonary edema

- Possible *pulmonary hypertension*



NSAIDS- closure of the PDA

- Usually closes on its own
- But in neonates
- Conservative management increasing pressure (ventilation) and restricting fluids
- Pharmacologic treatment with indomethacin, ibuprofen, acetaminophen
- Acetaminophen shows some promise in closing these, almost as effective

FDA recommends avoiding use of NSAIDs in pregnancy at 20 weeks or later because they can result in low amniotic fluid

NSAIDs may cause rare kidney problems in unborn babies

Drug Safety and Availability

Information about Nitrosamine Impurities in Medications

Drug Alerts and Statements

Medication Guides

Drug Safety Communications

Food and Drug Administration Overdose Prevention Framework

Drug Shortages

FDA Drug Safety Podcasts

Information by Drug Class

Medication Errors Related to CDER-Regulated Drug

9/1/2022 Update: The unapproved prescription NSAIDs salsalate and choline magnesium trisalicylate were added to Table 1.

10/16/2020 Update: This does not apply to NSAIDs administered directly to the eye.

en Español

Drug Safety Communication (PDF - 289KB)

10-15-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?

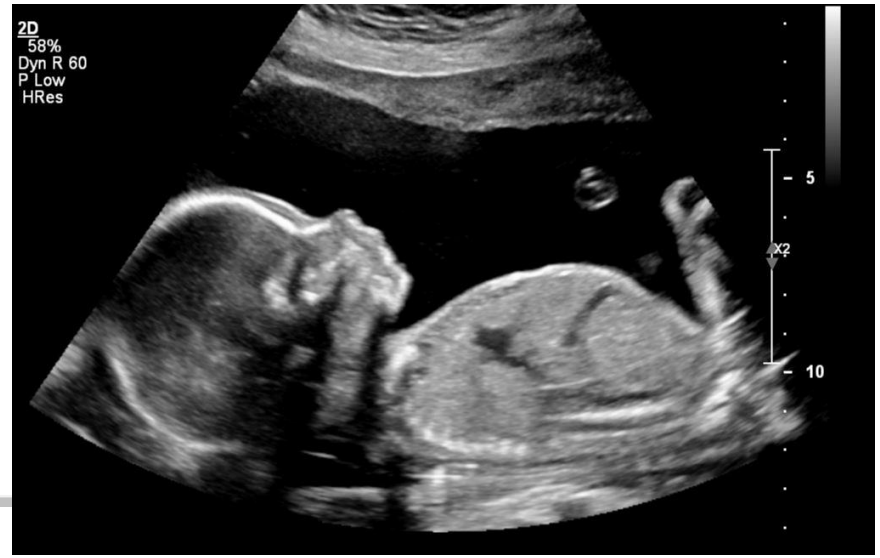
The U.S. Food and Drug Administration (FDA) is warning that use of nonsteroidal anti-inflammatory drugs (NSAIDs) around 20 weeks or later in pregnancy may cause rare but serious kidney problems in an unborn baby. This can lead to low levels of amniotic fluid surrounding the baby and possible complications. NSAIDs are commonly used to relieve pain and reduce fevers. They include medicines such as aspirin, ibuprofen, naproxen, diclofenac, and celecoxib. After around 20 weeks of pregnancy, the unborn babies' kidneys produce most of the amniotic fluid, so kidney problems can lead to low levels of this fluid. Amniotic fluid provides a protective cushion and helps the unborn babies' lungs, digestive system, and muscles develop.

Although this safety concern is well known among certain medical specialties, we wanted

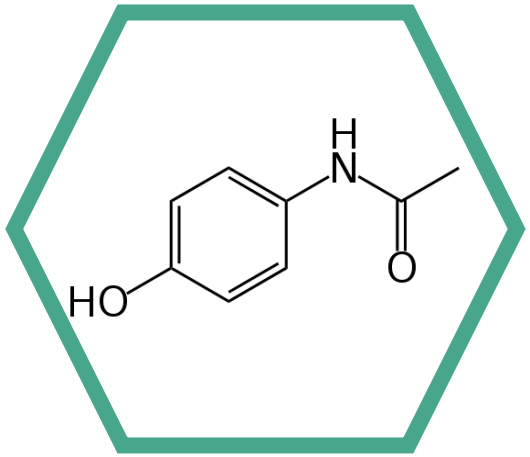
Content current as of:
09/01/2022

Regulated Product(s)
Drugs

Topic(s)
Safety - Issues, Errors, and Problems



Acetaminophen

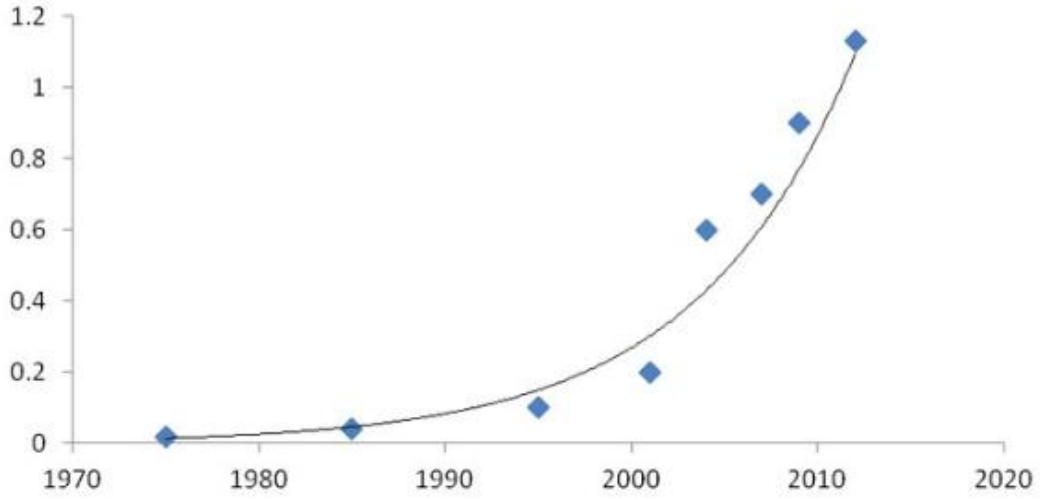


- Favorable safety profile
- No increased risk of congenital malformations, miscarriage, stillbirth
- Danish population-based cohort -risk for PTB among women using paracetamol in the third trimester (aHR 1.14, 95% confidence interval [CI] 1.03 to 1.26)
  - association may have been confounded by maternal conditions
  - Example: risk of preterm birth was increased among women with pre-eclampsia (adjusted hazard ratio 1.55, 95% CI 1.1.6 to 2.07) but not in women without pre-eclampsia (Rebordosa, 2009)
  - prenatal paracetamol exposure and asthma at 3 years (RR 1.13, 95% CI 1.02 to 1.25) and 7 years (RR 1.27, 95% CI 1.09 to 1.47), and these associations were similar after adjusting for maternal indications of respiratory tract infections, influenza, fever, or pain

Acetaminophen and ADHD or ASD? Problem

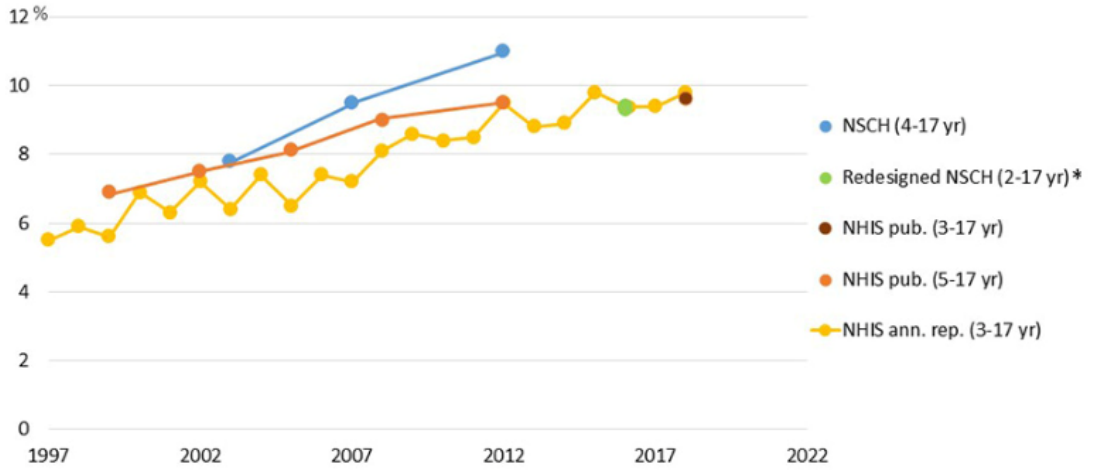
Dr. Yusuf Cem Kaplan' slides

Figure 2. The rising prevalence of autism spectrum disorders over 50 years. (Data from 'Autism Speaks' and CDC, USA) 24



ADHD diagnosis throughout the years: Estimates from published nationally representative survey data

(Percent of children with a parent-reported ADHD diagnosis)



- Change of diagnostic criteria?
- Changes in the methods of case identification and source of data?
- The frequency of acetaminophen use is around 60% in pregnant women (Bandoli et al. 2020)

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Co-Occurrence of Developmental Disorders: Children Who Share Symptoms of Autism, Dyslexia and Attention Deficit Hyperactivity Disorder

Ginny Russell and Zsuzsa Pavelka

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54159

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NEWS RELEASES

Media Advisory Wednesday, October 30, 2019

NIH-funded study suggests acetaminophen expos in pregnancy linked to higher risk of ADHD, autisı

What

Exposure to acetaminophen in the womb may increase a child's risk for attention deficit/hyperactivity disorder and autism spectrum disorder, suggests a study funded by the National Institutes of Health and the Agency for Health Care Research and Quality. The study was conducted by Xiaobing Wang, M.D., of the Johns Hopkins University Bloomberg School of Public Health, Baltimore, and colleagues. It appears in *JAMA Psychiatry*.

Search NI

Common painkiller should be investigated for possible risks to developing fetuses, experts say

By Sandee LaMotte, CNN

Updated 1815 GMT (0215 HKT) September 23, 2021

An international group of experts is cautioning against the use of acetaminophen during pregnancy until the pain killer is thoroughly investigated for potentially endangering fetal development.

More From CNN


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Health officials urge New Yorkers to get vaccinated after...

Woman claims Walmart's acetaminophen sales led to her kids' disorders

Lewis Kamb

ng cart. Photo: Bing Guan/Bloomberg via Getty Images

n federal court in Seattle this week for selling acetaminophen to
n, who claims her regular use of the medication during separate
and 2011 caused lifelong neurological disorders in her children.

SCIENCE · Published May 28, 2021 8:13pm EDT

Pain reliever acetaminophen linked to higher risk of autism, ADHD: study

The study based its findings on an analysis of 73,881 mother-child pairs in Europe

By Thomas Barrabi | Fox News

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HEALTHCARE & PHARMA OCTOBER 30, 2019 / 5:10 PM / UPDATED 3 YEARS AGO

Babies at higher risk for ADHD, autism if pregnant moms took acetaminophen

By Linda Carroll 4 MIN READ

(Reuters Health) - Babies born to women who used acetaminophen late in pregnancy may be at increased risk of ADHD and autism spectrum disorder, a new study suggests.

After examining stored blood samples from babies' umbilical cords, researchers determined that the risks of ADHD and autism were significantly increased in children whose blood had high levels of acetaminophen breakdown products, according to a report in JAMA Psychiatry.

Serious concerns

- Methodology
- Misclassification of timing, dose and duration
- Failure to account for confounding
- Genetic factors
- Other environmental factors
- Confounding by indication
- Other medications used

- Acetaminophen is used by 60% of pregnant women
  - Fever and migraines- both of which are associated with adverse effects and on fetal neurologic development
  - Those who utilize acetaminophen have higher prevalence of depression/anxiety, use of antidepressants

Paracetamol use in pregnancy — caution over causal inference from available data

Sura Alwan, Elizabeth A. Conover, Lorrie Harris-Sagaribay, Steven H. Lamm, Sharon V. Lavigne, Shari I. Lusskin, Sarah G. Obican, Alfred N. Romeo, Anthony R. Scialli and Katherine L. Wisner

The Consensus Statement by Bauer et al.[1] (Bauer, A. Z. et al. Paracetamol use during pregnancy — a call for precautionary action. *Nat. Rev. Endocrinol.* **17**, 757–766 (2021)[1]) has, not surprisingly, drawn considerable public attention. We agree with the authors' call for a focused research effort to investigate the reported associations from observational studies concerning prenatal use of paracetamol (also known as acetaminophen or *N*-acetyl-*p*-aminophenol (APAP)) and adverse reproductive and neurodevelopmental outcomes. However, we caution against an inference of causality that is based upon inadequate evidence. Here we provide a consensus counterstatement to the conclusion of that paper.

We reviewed the literature on APAP use in pregnancy and adverse outcomes. These studies are limited by serious methodological problems, including failure to account for confounding, and elements of bias that make interpretation of the data challenging. APAP is a neurodevelopmental and psychiatric conditions being passed from parent to child must also be considered[5,6]. An important problem in combining data from several observational studies is the considerable variability in selection and adjustment of the potential confounders, which intensifies interpretation challenges[7]. Finally, the quality and validity of neurodevelopmental outcome definitions are problematic[8]. Attempts to globally quantify neurodevelopmental outcome definitions for clinical interpretation can be highly misleading, given their wide phenotypic presentations.

Although the authors acknowledge the vast limitations of past studies on this subject, they do not consider the clinical consequences that could result from their premature precautionary statements. Currently, there exists vaccine hesitancy among a notable percentage of the population due to overinterpretation of flawed studies and unfounded associations. This vaccine hesitancy undoubtedly results in negative consequences for pregnant indi-

Sura Alwan[1]✉, Elizabeth A. Conover[2], Lorrie Harris-Sagaribay[3], Steven H. Lamm[4], Sharon V. Lavigne[5], Shari I. Lusskin[6], Sarah G. Obican[7], Alfred N. Romeo[8], Anthony R. Scialli[9] and Katherine L. Wisner[10]

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https://doi.org/10.1038/s41574-021-00606-x

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2. Bandoli, G., Palmsten, K. & Chambers, C. Acetaminophen use in pregnancy: examining prevalence, timing, and indication of use in a prospective birth cohort. *Paediatr. Perinat. Epidemiol.* **34**, 237–246 (2020).
3. Antoun, S. et al. Fever during pregnancy as a risk factor for neurodevelopmental disorders: results from a systematic review and meta-analysis. *Mol. Autism* **12**, 60 (2021).
4. Skajaa, N. et al. Pregnancy, birth, neonatal, and postnatal neurological outcomes after pregnancy with migraine. *Headache* **59**, 869–879 (2019).

Although the authors acknowledge the vast limitations of past studies on this subject, they do not consider the clinical consequences that could result from their premature precautionary statements.

Currently, there exists vaccine hesitancy among a notable percentage of the population due to overinterpretation of flawed studies and unfounded associations.

Alwan et al. 2021

Aspirin

- Aspirin and metabolite salicylate
- Not an established link for birth defects
- One case-control study reported no association between cardiac defects and first trimester exposure to aspirin after controlling for a range of possible confounders (Werler, 1989)
- No increased risk of miscarriage with adjusted odds ratios (aORs) ranging from 0.64 to 0.92 (Keim, 2006)
- High risk groups given aspirin to decrease risk of stillbirth
- Avoid high doses >500 mg due to associations with childhood asthma (7 years of age, Chu 2016) increased maternal bleeding (>650 mg), inadvertent closure of PDA

Aspirin use

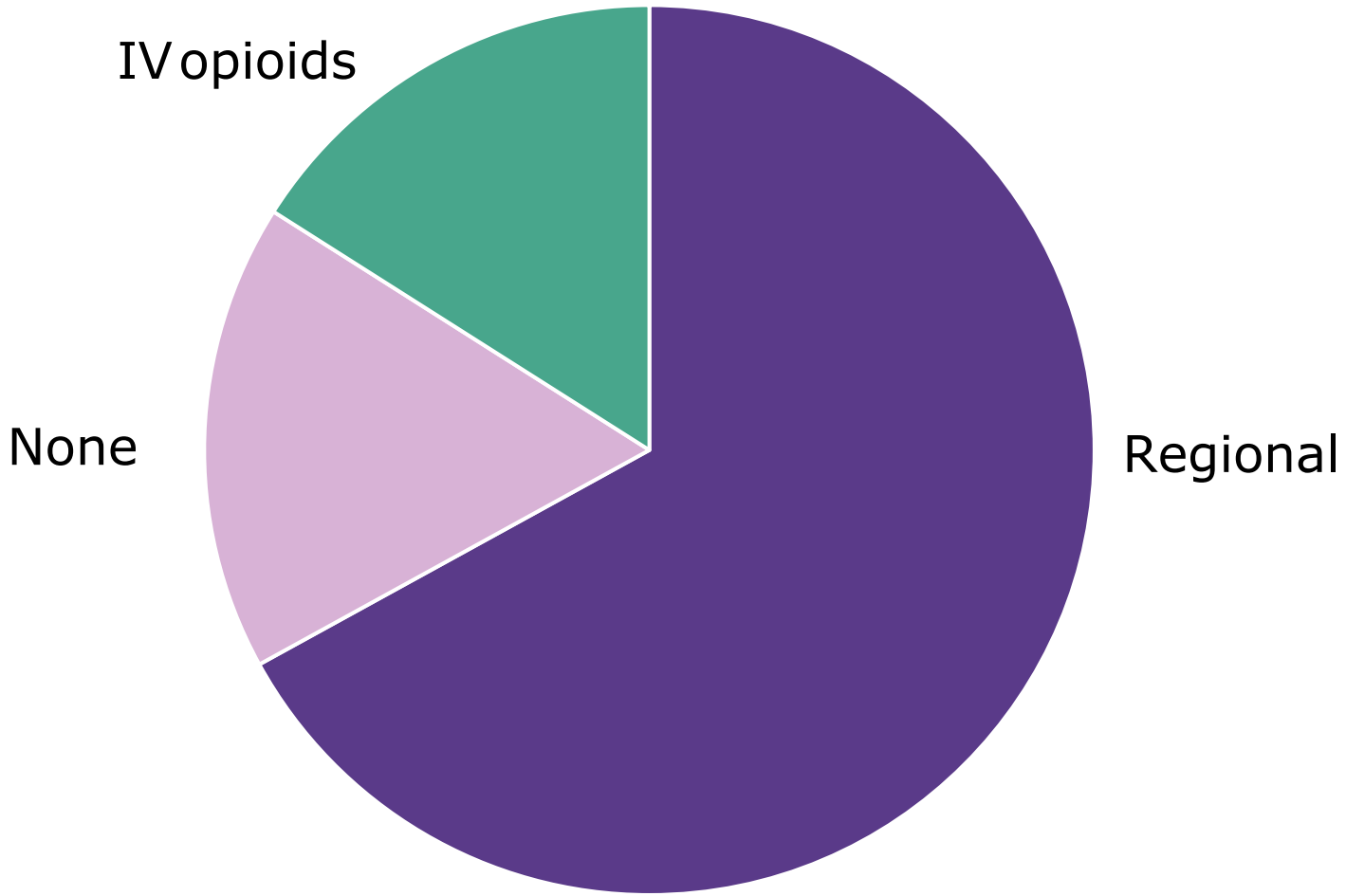
- LOW Dose Aspirin (81 mg vs 150 mg)
- ACOG, SMFM, USPSTF
- Prophylaxis for development of preeclampsia
- Initiate between 12-28 weeks (Optimal <16 weeks)
- Women at risk of preeclampsia:

  history of preeclampsia, multifetal gestation, renal disease, autoimmune disease, type 1 or type 2 diabetes, and chronic hypertension
- or *more than one* of several moderate-risk factors:

  first pregnancy, >35 years, a BMI>3030, family history of preeclampsia, sociodemographic characteristics

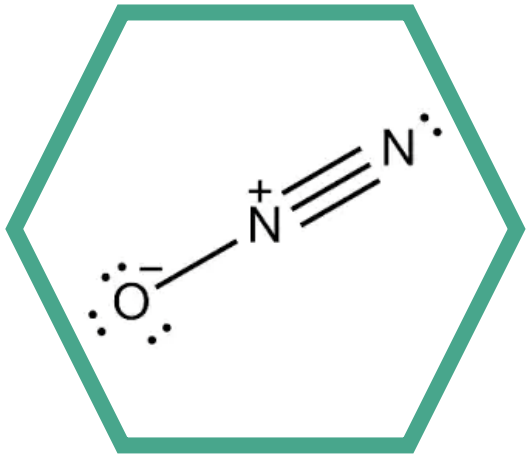
Intrapartum Pain Management

Labor Pain Management



1. Osterman MJ, Martin JA. Epidural and spinal anesthesia use during labor: 27-state reporting area, 2008. Natl Vital Stat Rep. 2011 Apr 6;59(5):1-13, 16.

Nitrous oxide (N2O)



- Self-administered, inhaled anesthetic gas
- 50/50 mix N2O/O2
  - Nitronox- administered with blender device
  - Etonox- administered from premixed canister
- Scavenging system limits environmental exposure
- Prevalent use in United Kingdom, Australia, New Zealand
  - Less common use in the United States

1. Rooks JP. Safety and risks of nitrous oxide labor analgesia: a review. J Midwifery Womens Health. 2011 Nov-Dec;56(6):557-65.
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Nitrous oxide- effectiveness

Advantages

- non-opioid
- preserves mobility
- does not affect labor progress
- higher labor satisfaction

Disadvantages

- maternal side effects (nausea, vomiting, dizziness, drowsiness)
- higher pain scores compared to epidural

1. Likis FE, Andrews JC, Collins MR, Lewis RM, Seroogy JJ, Starr SA, Walden RR, McPheeters ML. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg. 2014 Jan;118(1):153-67.
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Nitrous oxide- fetal exposure

- Intrapartum exposure
  - N2O readily crosses the placental interface
  - Rapid elimination of N2O by neonatal lungs with breathing
  - No difference in APGAR scores compared to other analgesia modalities
  - Studies have limited neonatal follow up period (birth to discharge)
  - Of 411 children with leukemia, higher association with N2O exposure (OR 1.3, 95% CI: 1.0-1.6)
- Occupational exposure
  - No increased risk for miscarriage when scavenging equipment used
  - No reproductive risk when used within parameters set for safe use

1. Likis FE, Andrews JC, Collins MR, Lewis RM, Seroogy JJ, Starr SA, Walden RR, McPheeters ML. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg. 2014 Jan;118(1):153-67.
2. Zack M, Adami H-O, Ericson A: Maternal and perinatal risk factors for childhood leukemia. Cancer Res 51:3696-3701, 1991.
3. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology. 2008 Oct;109(4):707-22.

Parenteral Opioids

Table 1. Commonly Used Parenteral or Systemic Opioids for Labor Analgesia

Drug	Dosage and Route of Delivery	Onset	Duration	Elimination Half-life (Maternal)
Fentanyl	50–100 micrograms (every hour); Alternatively, as PCA, load 50 micrograms, then 10–25 micrograms Q 10–12 minutes	2–4 minutes IV	30–60 minutes	3 hours
Morphine	2–5 mg (IV); 5–10 mg (IM)	10 minutes (IV); 30 minutes (IM)	1–3 hours	2 hours
Nalbuphine	10–20 mg IV, SQ, or IM	2–3 minutes IV; 15 minutes SQ or IM	2–4 hours	2–5 hours
Butorphanol	1–2 mg IV or IM	5–10 minutes IV; 30–60 minutes IM	4–6 hours	2–5 hours
Remifentanil	0.15–0.5 micrograms/ kg Q 2 minutes as PCA	20–90 seconds	3–4 minutes	9–10 minutes

Abbreviations: IM, intramuscularly; IV, intravenously; PCA, patient-controlled analgesia; Q, every; SQ, subcutaneous.

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 209: Obstetric Analgesia and Anesthesia. Obstet Gynecol. 2019 Mar;133(3):e208-e225.

Neonatal effects of intrapartum opioids

In general, greater effects with parenteral vs. neuraxial:


Low Apgar scores


Respiratory depression

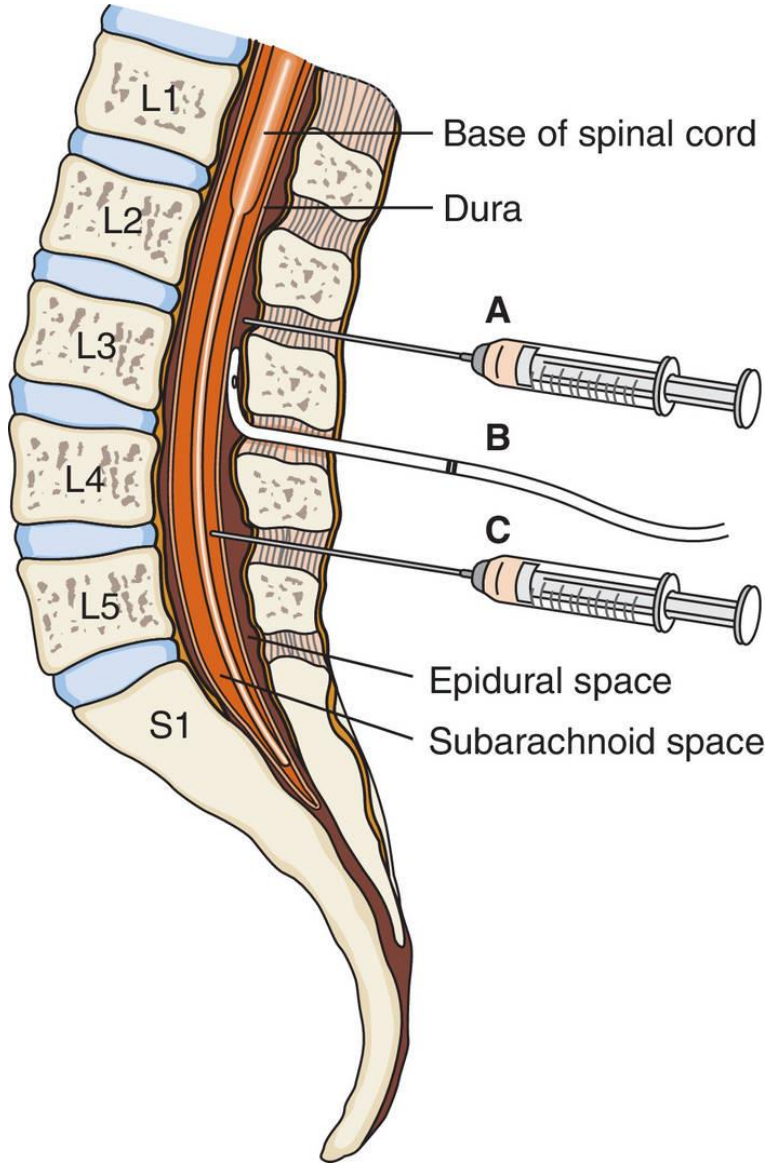

Low muscle tone


Poor suckling

1. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 209: Obstetric Analgesia and Anesthesia. Obstet Gynecol. 2019 Mar;133(3):e208-e225.

Neuraxial analgesia

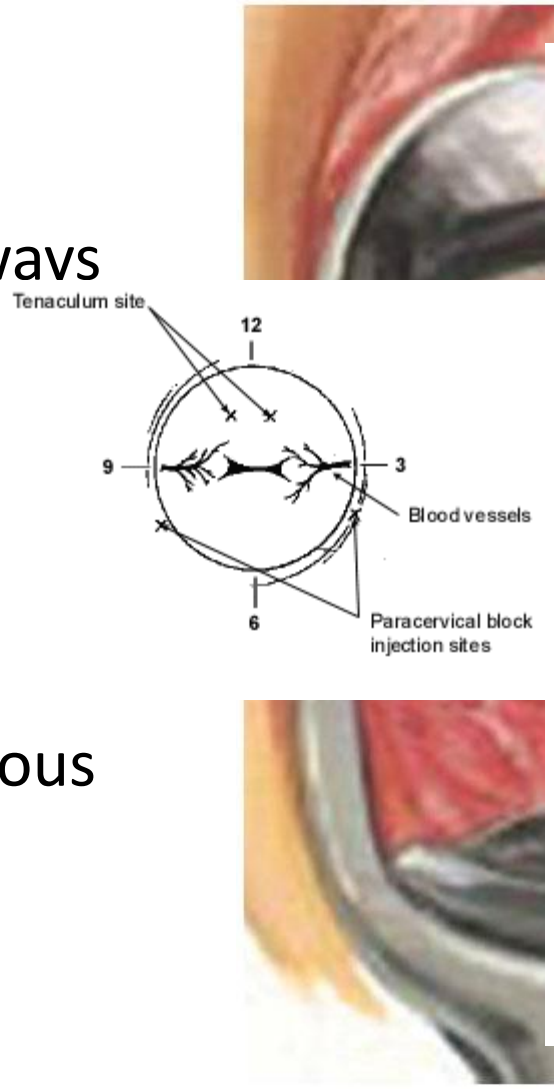
- Epidural, Spinal, and Combined Spinal-Epidural
  - Better pain scores compared with IV opioids
- Combination of two agents
  - Dilute local anesthetic (bupivacaine, ropivacaine)
  - Lipophilic opioid (fentanyl, sufentanil)

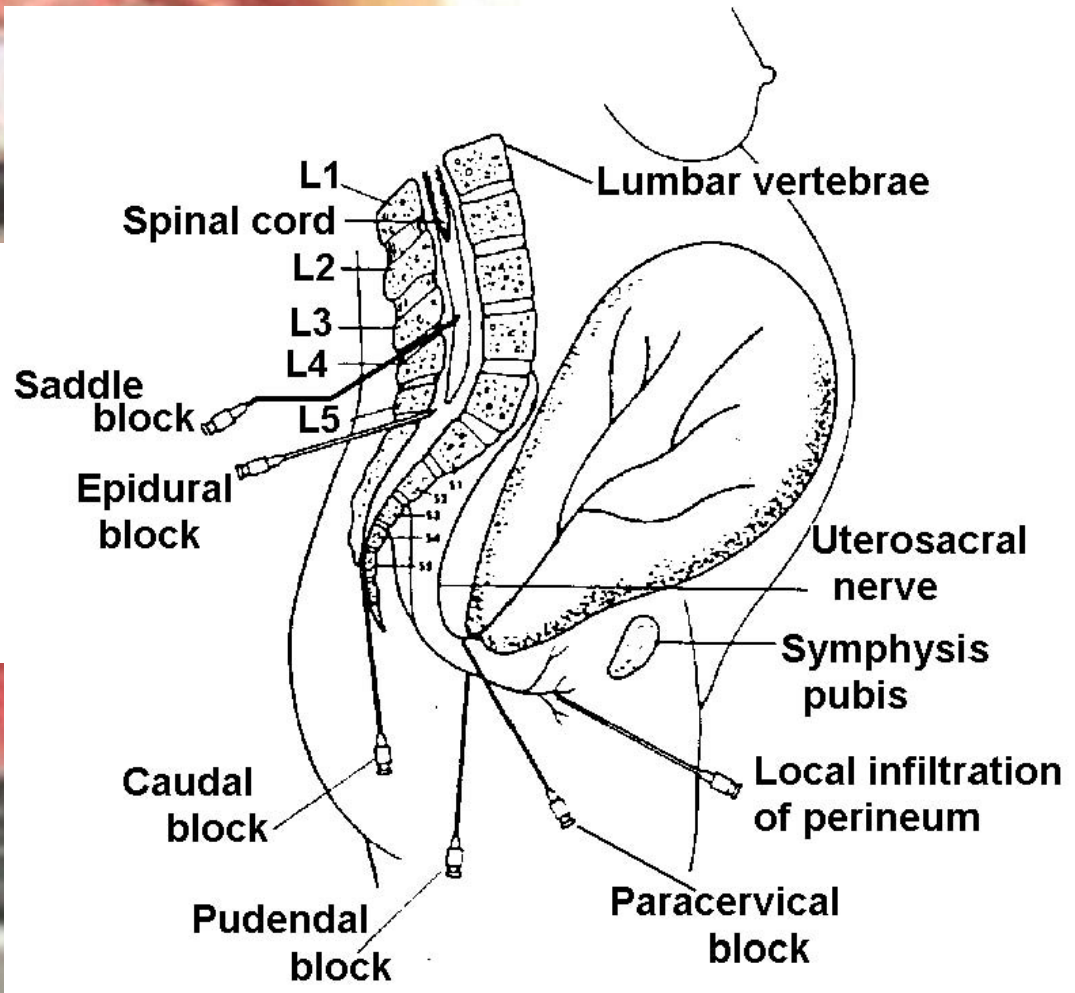


1. Nanji JA, Carvalho B. Pain management during labor and vaginal birth. Best Pract Res Clin Obstet Gynaecol. 2020 Aug;67:100-112.

Bilateral Paracervical block

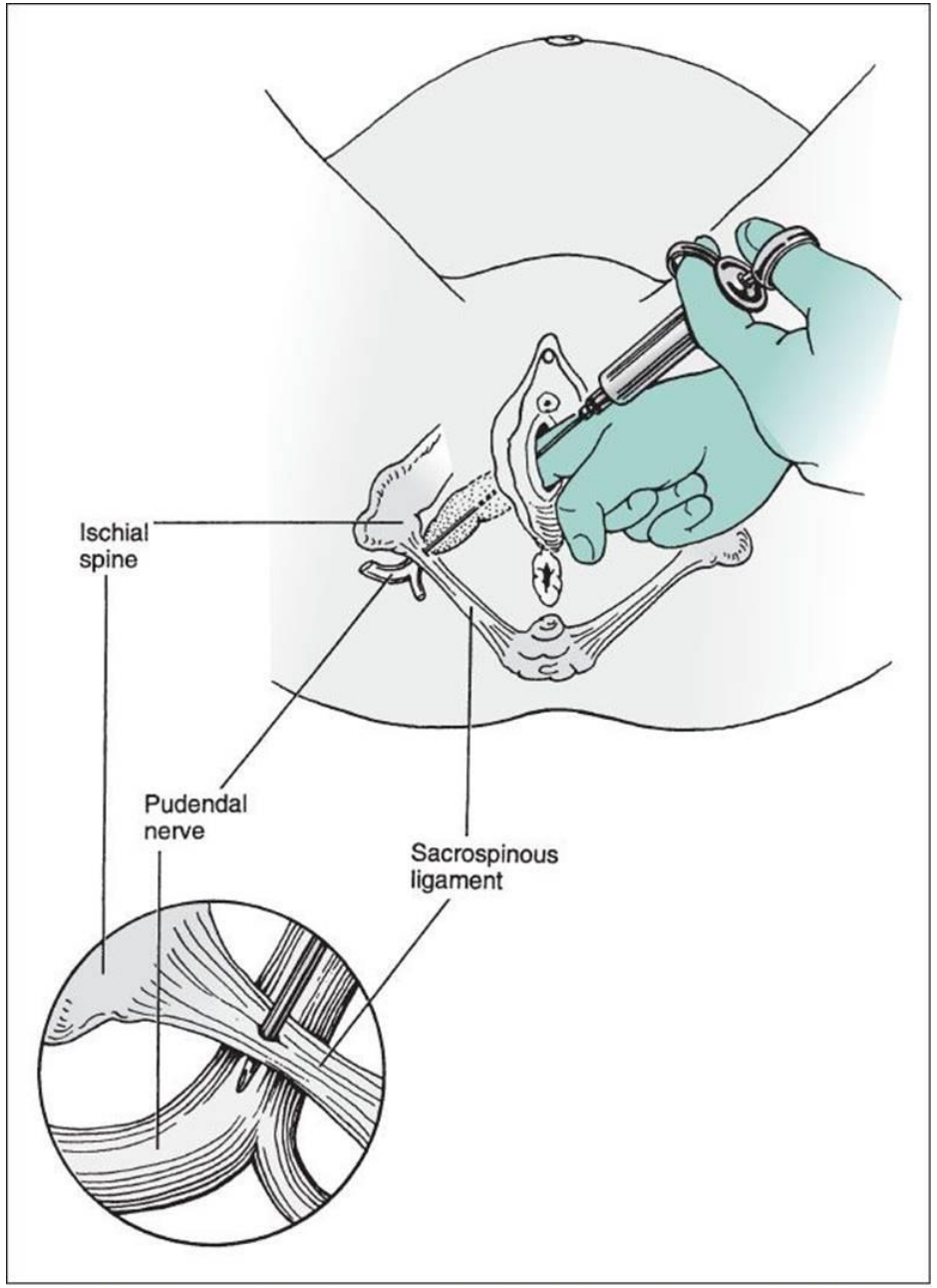
- Interrupts uterine nociceptive pain pathwavs T10- L1
- First stage of labor
- No perineal relief
- 5mg/kg 1% lidocaine (r epinephrine)
- Uterine artery and venous plexus is so close, may increase uptake by mother/fetus





Pudendal block

- For those who do not desire an epidural
- Effective for second and third stages of labor
- Blocking sacral nerves S3, S4, S5
- Transvaginal approach- needle behind the sacrospinous ligament aiming toward the ischial spine
- 5mg/kg of lidocaine (1% without epinephrine)
- Onset of action 3-5 min



Beckman, Obstetrics and Gynecology 2002

Prenatal Opioids

Definitions

Prenatal Opioid Exposure (POE)- any exposure to opioids, whether prescription or illicit, during pregnancy

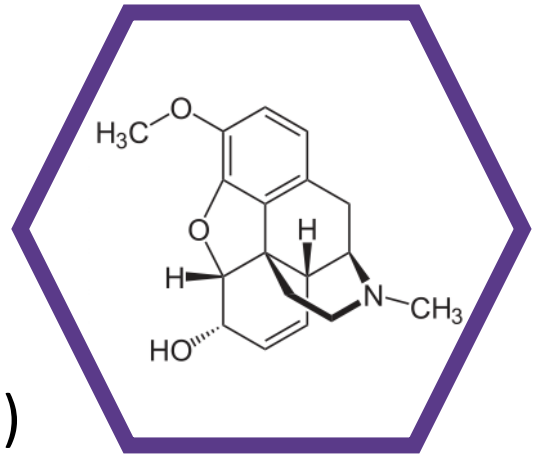
-Chronic pain

-Post-procedural / post-surgical

Opioid Use Disorder (OUD)- chronic disease characterized by tolerance, craving, inability to control use, and continued use of opioids despite adverse consequences

1. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics*. 2015;135(5):842-850.
2. Committee Opinion No. 711: Opioid Use and Opioid Use Disorder in Pregnancy. Obstet Gynecol. 2017 Aug;130(2):e81-e94.

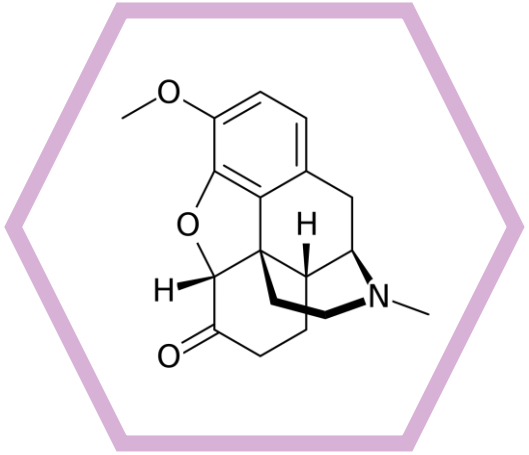
Codeine



- Often used as antitussive or as combination drug for pain (Tylenol #3)
- Metabolized to morphine by CYP450 enzyme CYP2D6.
- The Norwegian Mother and Child Cohort Study:
  - 2,666 pregnancies with codeine use and 65,316 without any opioid exposure
  - No difference in survival (aOR 0.9, 95% CI: 0.6-1.5)
  - No difference in congenital malformations (aOR 0.9, 95% CI: 0.8-1.1)
- Retrospective studies of first-trimester codeine use *inconsistently* associated with respiratory tract malformation, pyloric stenosis, inguinal hernia, cardiac defects, cleft lip and palate, and neural tube defects.

1. Nezvalov-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. Eur J Clin Pharmacol. 2011;67(12):1253-1261.
2. Heinonen OP et al: Birth Defects and Drugs in Pregnancy, Littleton, Publishing Sciences Group, pp 287-95, 1977.
3. Bracken MB, Holford TR: Exposure to prescribed drugs in pregnancy and association with congenital malformations. Obstet Gynecol 58:336-44, 1981.
4. Saxen I: Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol 4:37-44, 1975.
5. Rothman KJ et al: Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 109:433-9, 1979.

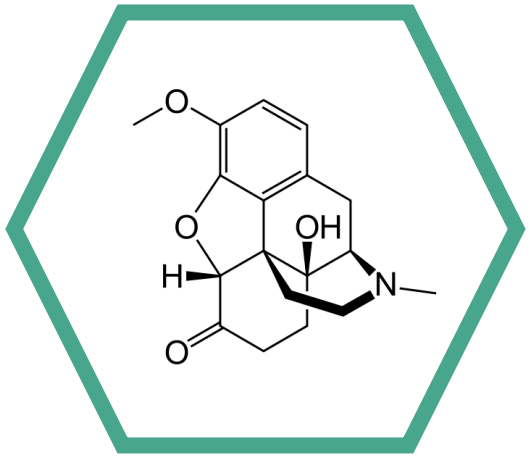
Hydrocodone



- Most dispensed opioid during pregnancy from 2005-2011
- Combination drug: Vicodin (hydrocodone/acetaminophen)
- Animal data
  - Cranioschisis observed in hamsters receiving 100x human dose
- Human data demonstrating no increased risk of congenital anomalies
  - Collaborative Perinatal Project: n=60 (12)
  - Teratology information services: n=40

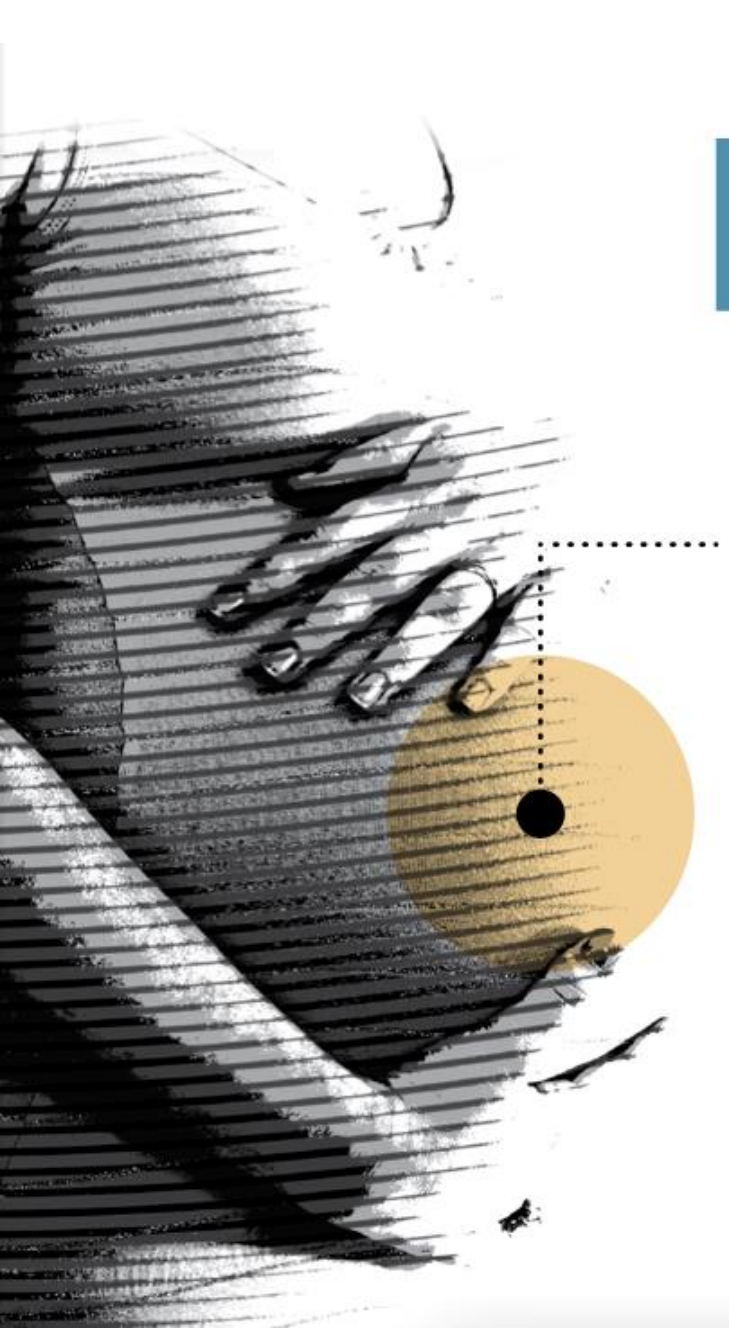
1. Bateman BT, Hernandez-Diaz S, Rathmell JP, et al: Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. Anesthesiology. 2014;120(5):1216-24,
2. Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Publishing Sciences Group Inc., Littleton, MA, pp 287, 434, 1977.
3. Schick B, Hom M, Tolosa J, Librizzi R. Donnenfeld A. Preliminary analysis of first trimester exposure to oxycodone and hydrocodone. Reprod Toxicol. 1996;10:162.

Oxycodone



- Combination drug: Percocet (oxycodone/acetaminophen)
- Data limited to case series:
  - 8 pregnancies with no increased risk
  - 78 pregnancies contacting teratology information services (first-trimester)

1. Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Publishing Sciences Group Inc., Littleton, MA, 1977.
2. Schick B, Hom M, Tolosa J, Librizzi R. Donnenfeld A. Preliminary analysis of first trimester exposure to oxycodone and hydrocodone. Reprod Toxicol. 1996;10:162.



ARE OPIOID PAIN MEDICATIONS SAFE FOR WOMEN WHO ARE PREGNANT OR PLANNING TO BECOME PREGNANT?

Possible risks to your pregnancy include[1,2]:

- **Neonatal Opioid Withdrawal Syndrome (NOWS):** withdrawal symptoms (irritability, seizures, vomiting, diarrhea, fever, and poor feeding) in newborns[3]
- **Neural tube defects:** serious problems in the development (or formation) of the fetus' brain or spine
- **Congenital heart defects:** problems affecting how the fetus' heart develops or how it works
- **Gastroschisis:** birth defect of developing baby's abdomen (belly) or where the intestines stick outside of the body through a hole beside the belly button
- **Stillbirth:** the loss of a pregnancy after 20 or more weeks
- **Preterm delivery:** a birth before 37 weeks

1. Centers for Disease Control and Prevention. Pregnancy and Opioid Pain Medication. U.S. Department of Health and Human Services. Accessed 10 Oct, 2022.

Congenital anomalies

RESEARCH www.AJOG.org

OBSTETRICS

Maternal treatment with opioid analgesics and risk for birth defects

Cheryl S. Broussard, PhD; Sonja A. Rasmussen, MD, MS; Jennita Reefhuis, PhD; Jan M. Friedman, MD, PhD; Michael W. Jann, PharmD; Tiffany Riehle-Colarusso, MD, MSE; Margaret A. Honein, PhD, MPH; for the National Birth Defects Prevention Study

- Data from National Birth Defects Prevention Study (1997-2005)
- Exposure:
  - retrospective self-report of mothers
  - 1 or more therapeutic use of opioids (any dose, duration, or frequency)
  - Exposure 1 month prior to and 3 months after conception
  - **Codeine**, **hydrocodone**, meperidine, oxycodone
- Outcome: birth defect

1. Broussard CS, Rasmussen SA, Reefhuis J, Friedman JM, Jann MW, Riehle-Colarusso T, Honein MA; National Birth Defects Prevention Study. Maternal treatment with opioid analgesics and risk for birth defects. Am J Obstet Gynecol. 2011 Apr;204(4):314.e1-11.

TABLE 2
Associations between maternal opioid analgesic treatment and specific major birth defects

Birth defect	Total no.[a]	No. exposed	aOR (95% CI)
Hypothesis-testing analysis			
Controls	6701	134	Referent
Anencephaly/craniorachischisis	340	9	1.7 (0.84–3.4)
Spina bifida	718	26	2.0 (1.3–3.2)
Any of included heart defects	7724	211	1.4 (1.1–1.7)
Laterality defects with CHD	198	4	1.2 (0.42–3.2)
Atrioventricular septal defect	175	9	2.4 (1.2–4.8)
Anomalous pulmonary venous return	206	4	0.71 (0.22–2.3)
Single ventricle/complex	201	4	1.1 (0.42–3.2)
Conotruncal defects	1481	41	1.5 (1.0–2.1)
Tetralogy of Fallot	672	21	1.7 (1.1–2.8)
D-transposition of great arteries	461	10	1.1 (0.56–2.1)
Ventricular septal defect conoventricular	110	6	2.7 (1.1–6.3)
Left ventricular outflow tract obstruction defects	1195	36	1.5 (1.0–2.2)
Hypoplastic left heart syndrome	357	17	2.4 (1.4–4.1)
Coarctation of aorta	630	11	0.88 (0.47–1.6)
Aortic stenosis	253	7	1.3 (0.61–2.9)
Right ventricular outflow tract obstruction defects	1175	40	1.6 (1.1–2.3)
Pulmonary valve stenosis	867	34	1.7 (1.2–2.6)
Septal defects	3482	87	1.2 (0.93–1.6)
Ventricular septal defect perimembranous	1402	29	0.99 (0.65–1.5)
Atrial septal defect secundum	1507	43	1.3 (0.94–1.9)
Atrial septal defect not otherwise specified	511	17	2.0 (1.2–3.6)
CHD association: ventricular septal defect + atrial septal defect	528	17	1.7 (1.0–2.9)
CHD association: pulmonary valve stenosis + ventricular septal defect	131	4	1.3 (0.46–3.7)
Cleft palate	936	25	1.3 (0.84–2.0)
Cleft lip with cleft palate	1162	33	1.4 (0.96–2.1)
Cleft lip without cleft palate	614	9	0.68 (0.34–1.3)

Broussard. Opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011.

(continued)

TABLE 2
Associations between maternal opioid analgesic treatment and specific major birth defects *(continued)*

Birth defect	Total no.[a]	No. exposed	aOR (95% CI)
Exploratory analysis			
Controls	6701	134	Referent
Amniotic band syndrome/limb body wall complex	203	5	1.0 (0.37–2.9)
Hydrocephaly	301	11	2.0 (1.0–3.7)
Cataracts	217	7	1.6 (0.72–3.5)
Glaucoma/anterior chamber defects	103	5	2.6 (1.0–6.6)
Anotia/microtia	403	4	0.77 (0.28–2.1)
Esophageal atresia	434	12	1.4 (0.76–2.5)
Intestinal atresia/stenosis	266	4	0.88 (0.32–2.4)
Anorectal atresia/stenosis	623	18	1.5 (0.87–2.4)
Hypospadias second/third degree	1313	29	0.92 (0.59–1.4)
Bilateral renal agenesis or hypoplasia	112	4	1.3 (0.40–4.2)
Longitudinal limb deficiency	269	6	1.1 (0.49–2.6)
Longitudinal preaxial limb deficiency	157	4	1.3 (0.48–3.6)
Transverse limb deficiency	415	7	1.0 (0.46–2.2)
Craniosynostosis	806	16	0.82 (0.48–1.4)
Diaphragmatic hernia	507	12	1.2 (0.66–2.2)
Omphalocele	267	7	1.3 (0.60–2.8)
Gastroschisis	726	26	1.8 (1.1–2.9)

Odds ratios were adjusted for maternal age, race/ethnicity, education, presence or absence of prepregnancy obesity, presence or absence of periconceptional smoking, and study center.
aOR, adjusted odds ratio; *CHD*, congenital heart defect; *CI*, confidence interval.

[a] Some comparisons used fewer than total number of controls (eg, hypospadias only used male controls); number of cases includes those with nonmissing exposure data and excludes prepregnancy diabetics (type 1 or 2) and mothers reporting exposure to opioid street drugs.

Broussard. Opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011.

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Associations between maternal opioid analgesic treatment and specific major birth defects

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Broussard. Opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011. (continued)

Conoventricular septal defects **OR 2.7**, 95% CI: 1.1-6.3

Atrioventricular septal defects **OR 2.0**, 95% CI: 1.2-3.6

Hypoplastic left heart **OR 2.4**, 95% CI: 1.4-4.1

Spina bifida **OR 2.0**, 95% CI: 1.3-3.2

Gastroschisis **OR 1.8**, 95% CI 1.1-2.9

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Associations between maternal opioid analgesic treatment and specific major birth defects *(continued)*

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Broussard. Opioid analgesics and risk for birth defects. Am J Obstet Gynecol 2011.

Limitations

- Recall bias
  - Interviews occurred at an average of 9-11 months after EDD
  - Some recalling up to 3 years after exposure
- Exposure did not consider dose, duration, frequency
- Most exposures were from surgical procedures
- Other comorbidities as exposures were not controlled for (eg: diabetes)

Other birth outcomes

- Administrative data from Ontario healthcare system
  - Excluded people with opioid use disorder
- Exposures: fentanyl, hydrocodone, morphine, oxycodone, tramadol, codeine, oxycodone
- Confounders: age, parity, SES, diabetes, obstetric comorbidity score, obesity, hypertension, pain, co-prescribed, benzodiazepine/ barbiturate, delivery year.

1. Brogly SB, Velez MP, Werler MM, Li W, Camden A, Guttmann A. Prenatal Opioid Analgesics and the Risk of Adverse Birth Outcomes. Epidemiology. 2021 May 1;32(3):448-456.

Association Between Any Prenatal Opioid Analgesic Exposure and Birth Outcomes

Outcome		No. of infants (exposure)	No. of infants (outcome)	Adjusted Risk Ratio (95% CI)
Preterm birth	Any opioid	25,755	2,693	**1.3 (1.2, 1.3)**
	None	601,417	43,213	REF
SGA birth	Any opioid	25,064	2,402	1.0 (0.9, 1.0)
	None	589,133	57,255	REF
Stillbirth	Any opioid	25,725	235	**1.6 (1.4, 1.8)**
	Non	601,047	3,536	REF

Adapted from Brogly et al.

Opioids and breastfeeding

- Difficulty suckling
- Drowsiness (inefficient elimination)
- Central nervous system depression (ultra-rapid metabolizers)
  - Avoid codeine (FDA)
  - Oxycodone >30mg/d not recommended
  - Monitor for drowsiness, sedation, feeding difficulty, limpness

1. National Opioid Use Guideline Group. Canadian guideline for safe and effective use of opioids for chronic non-cancer pain; 2010. Available at: http://nationalpaincentre.mcmaster.ca/opioid/ documents.html.

Opioid Use Disorder

The pregnancy opioid epidemic

- 2007: 22.8% Medicaid patients filled opioid Rx during pregnancy
- Antepartum opioid use increased 5x from 2000-2009
- Neonatal abstinence syndrome increased from 1.5/1000 births (1999) to 6.0/1000 births (2013)

Pregnancy-Related Deaths: Data from Maternal Mortality Review Committees in 36 US States, 2017–2019

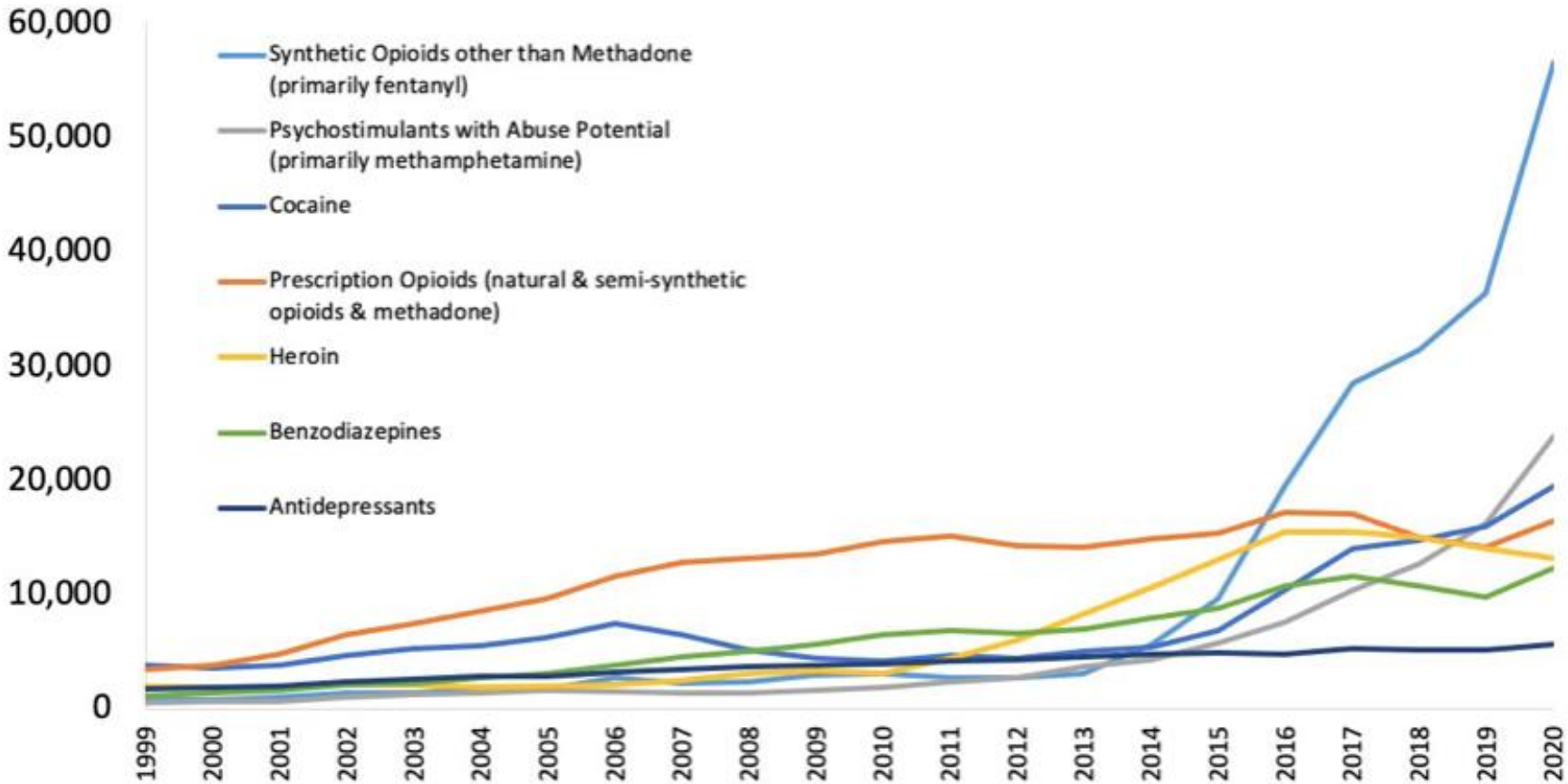
MMRIA MATERNAL MORTALITY REVIEW INFORMATION APP

Susanna Trost, MPH; Jennifer Beauregard, MPH, PhD; Gyan Chandra, MS, MBA; Fanny Njie, MPH; Jasmine Berry, MPH; Alyssa Harvey, BS; David A. Goodman, MS, PhD

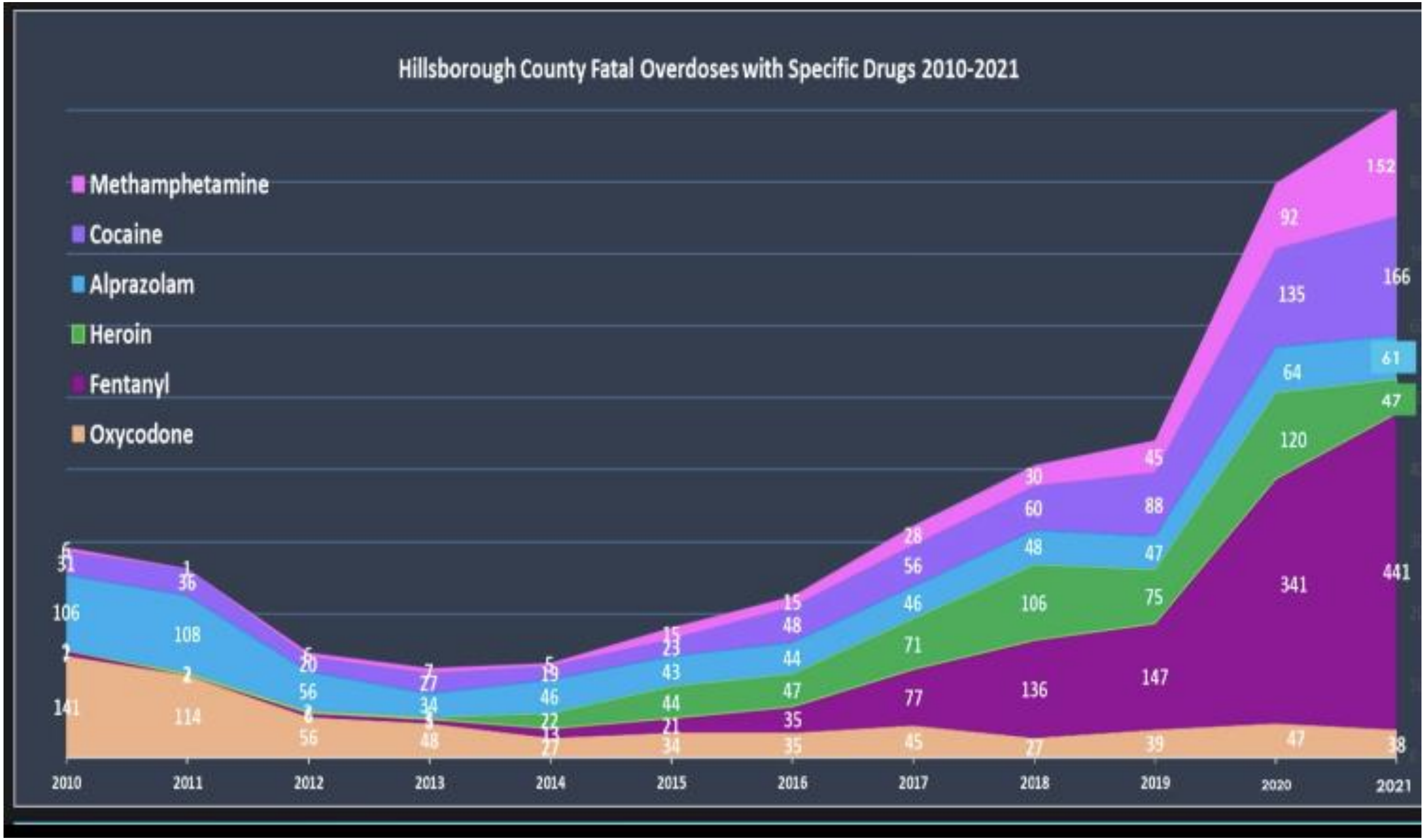
Table 4. Underlying causes of pregnancy-related deaths*, overall and by race or ethnicity[1], data from Maternal Mortality Review Committees in 36 US states, 2017–2019[1]

	Total		Hispanic		Non Hispanic									
					AIAN		Asian		Black		NHOPI		White	
	N	%	n	%	n	%	n	%	n	%	n	%	n	%
Mental health conditions[2]	224	22.7	34	24.1	2	-	1	3.1	21	7.0	0	-	159	34.8
Hemorrhage[3]	135	13.7	30	21.3	2	-	10	31.3	33	10.9	1	-	53	11.6
Cardiac and coronary conditions[4]	126	12.8	15	10.6	1	-	7	21.9	48	15.9	0	-	49	10.7
Infection	91	9.2	15	10.6	1	-	0	0.0	23	7.6	0	-	49	10.7
Embolism-thrombotic	86	8.7	9	6.4	0	-	2	6.3	36	11.9	0	-	34	7.4
Cardiomyopathy	84	8.5	5	3.6	0	-	2	6.3	42	13.9	0	-	33	7.2
Hypertensive disorders of pregnancy	64	6.5	7	5.0	0	-	1	3.1	30	9.9	1	-	22	4.8

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020

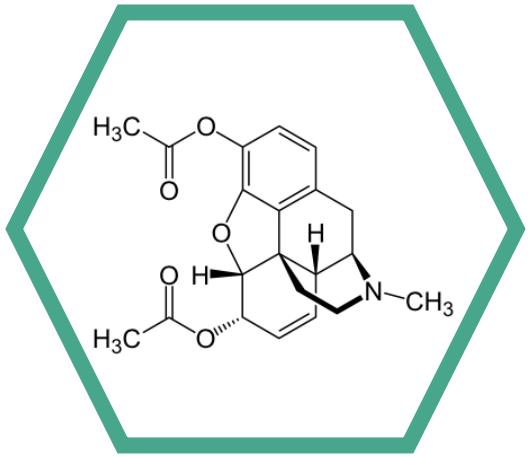


*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.



Hillsborough County Fatal Overdoses with Specific Drugs 2010-2021
Methamphetamine
Cocaine
Alprazolam
Heroin
Fentanyl
Oxycodone
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021

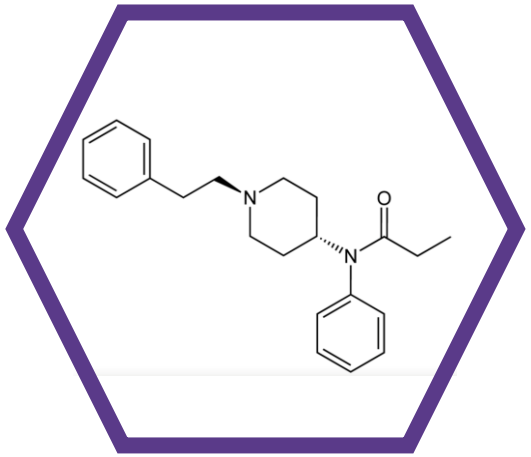
Heroin



- No described birth defect syndrome
- Associated with pregnancy complications in humans
  - Preterm delivery
  - Fetal growth restriction
  - Meconium-stained amniotic fluid
  - Perinatal death
- Studies assessing magnitude of exposure effect limited by inadequate control population and confounding

1- Ostrea EM, Chavez CJ: Perinatal problems (excluding neonatal withdrawal) in maternal drug addiction: a study of 830 cases. J Pediatr 94:292-5, 1979.
2- Naeye RL et al: Fetal complications of maternal heroin addiction: abnormal growth, infections and episodes of stress. J Pediatr 83:1055-61, 1973.
3- Little BB, Snell LM, Klein VR et al: Maternal and fetal effects of heroin addiction during pregnancy. J Reprod Med 35: 159-62, 1990.
4- Fajemirokun-Odudeyi O, Sinha C, Tutty S et al: Pregnancy outcome in women who use opiates. Eur J Obstet Gynecol Reprod Biol. 2006;126(2):170-5.

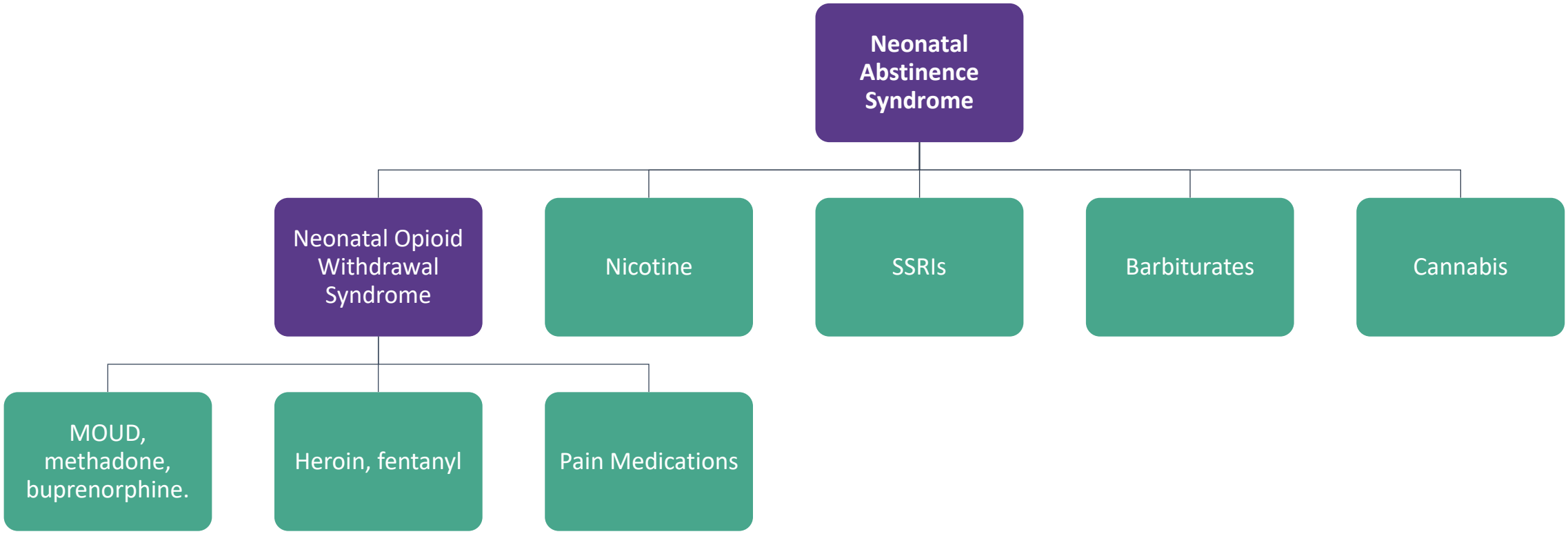
Fentanyl



- No increased risk malformations in rats at extreme doses
- Cheap production cost
  - 1 kg heroin = $50,000
  - 1 kg fentanyl = $3,000
  - Added or mixed with most illicit drugs
- High potency
  - 50x potency heroin
  - 100x potency heroin

1- Fujinaga M et al: Reproductive and teratogenic effects of fentanyl in Sprague-Dawley rats. Teratology 34:51-7, 1986
2- DEA.gov

Neonatal Abstinence Syndrome


Neonatal Abstinence Syndrome
Neonatal Opioid Withdrawal Syndrome
Nicotine
SSRIs
Barbiturates
Cannabis
MOUD, methadone, buprenorphine.
Heroin, fentanyl
Pain Medications

Neonatal Opioid Withdrawal Syndrome

- Symptoms: irritability, high-pitched cry, poor sleep, poor feeding
- Onset: 2-4 days after delivery
- Nicotine, SSRIs, and benzodiazepines may contribute to more severe presentation of NOWS

Anticipated Timing of Withdrawal Symptoms

	DRUG	SYMPTOM ONSET	PEAK IN SYMPTOMS	START TO IMPROVE
OPIOIDS	Short-acting opioids[2]	1st 24 hours	~36 hours	~48 hours (day 2)
	Heroin	~24 hours	~36 hours	~48 hours (day 2)
	Methadone	48-72 hours (day 2-3)	~72-96 hours (day 3-4)	~96-120 hours (day 4-5)
	Buprenorphine	36-60 hours	~72-96 hours (day 3-4)	~96-120 hours (day 4-5)
NON-OPIOIDS	Nicotine	1st 24 hours	~24-48 hours (day 1-2)	~48 hours (day 2)
	SSRIs	24-48 hours (day 1-2)	~48 hours (day 2)	48-72 hours (day 2-3)

Treating NOWS

- Nonpharmacologic Interventions

+

- Pharmacologic Treatment

Pharmacologic Treatment

- Treatment designed to prevent death and seizures while permitting the infant to eat and sleep with less irritability
- Oral Morphine vs. Oral Methadone
- Sublingual Buprenorphine
- Adjunctive Agents (phenobarbital, clonidine)

Non-pharmacologic Interventions

Rooming in

Parent/caregiver presence

S2S contact

Holding

Safe/effective swaddling

Optimal feeding

Non-nutritive sucking

Quiet, low light environment

Rhythmic movement

Additional help/support

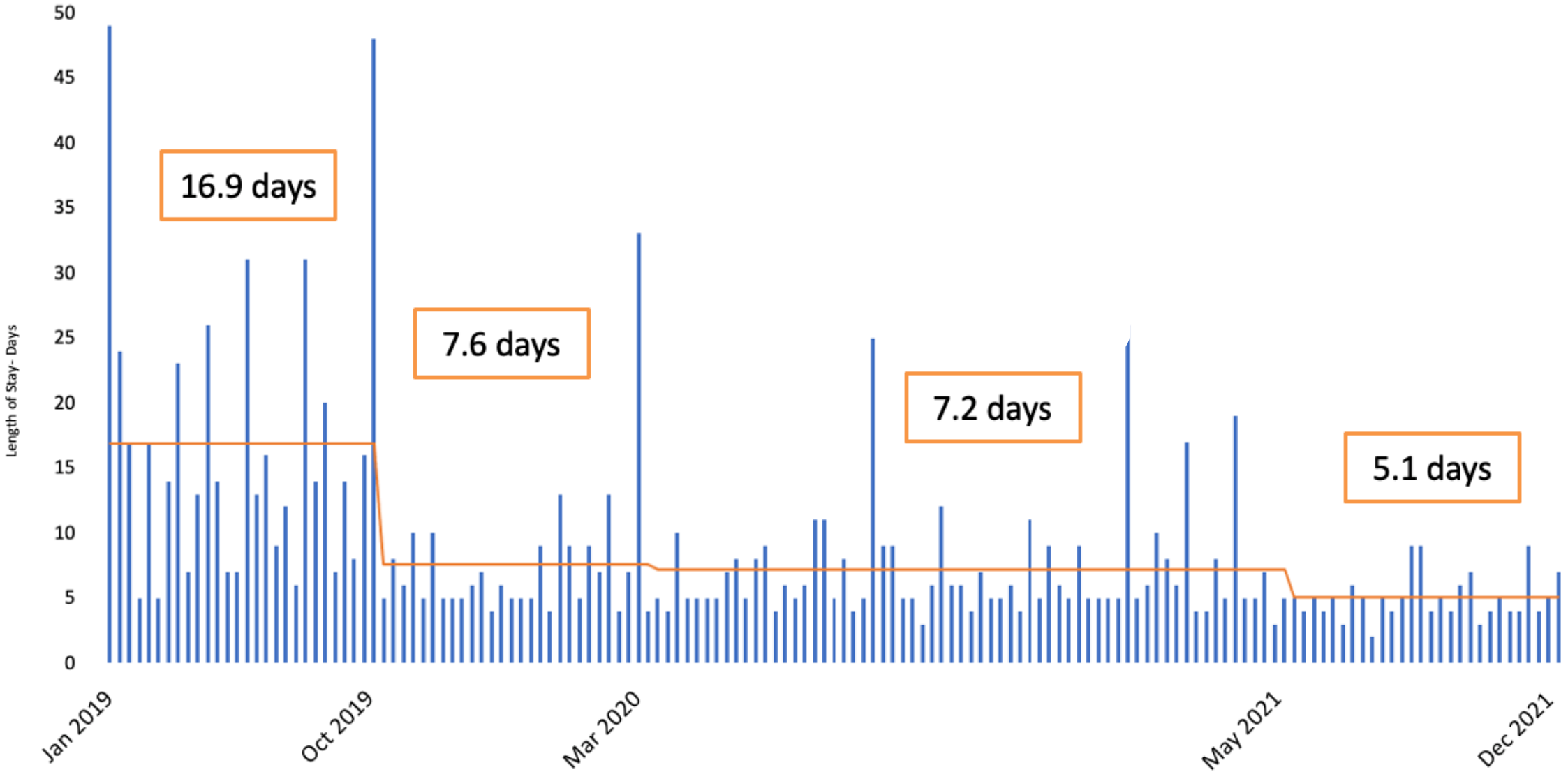
Limit visitors

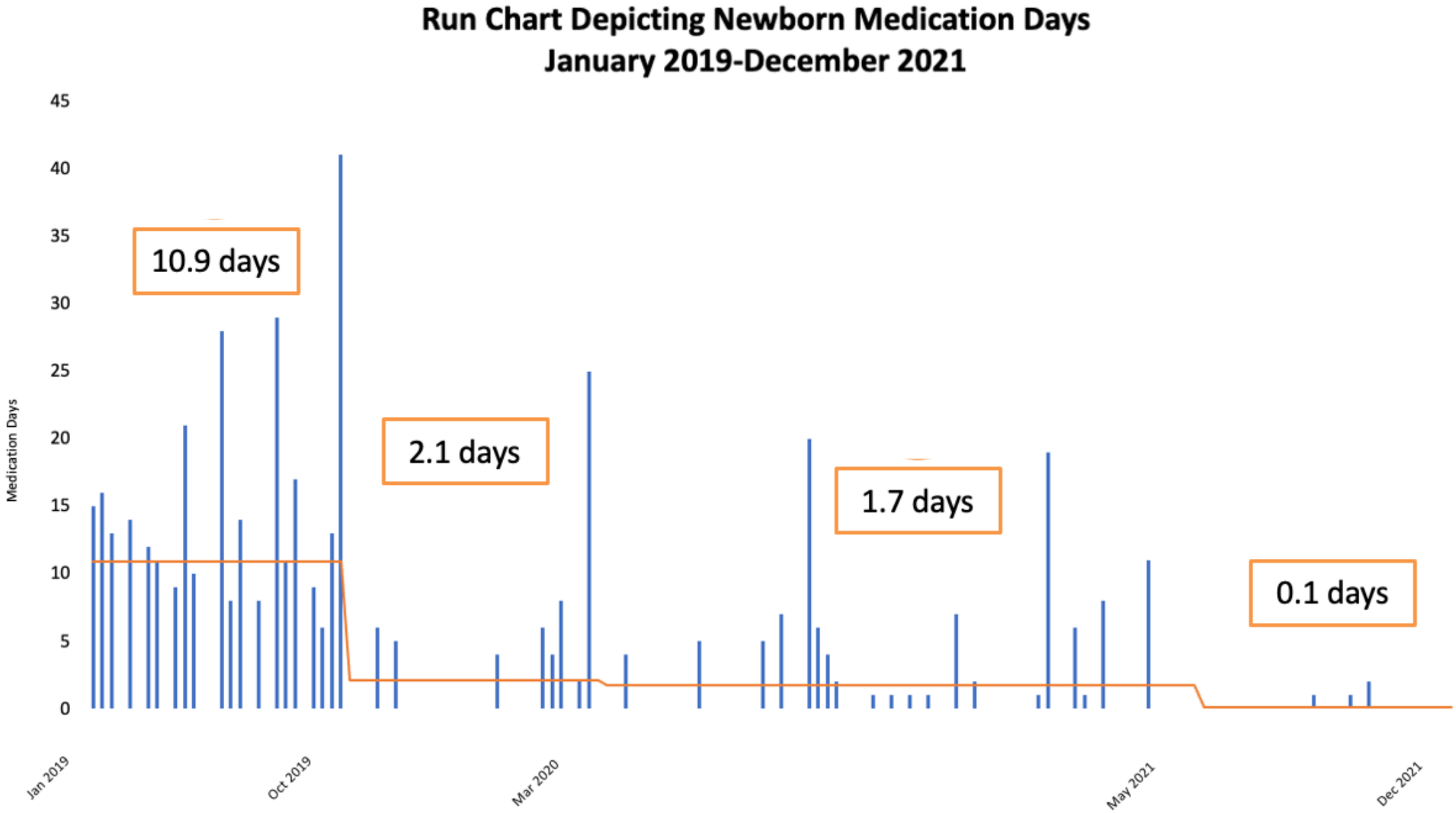
Cluster care & assessments

Safe sleep/fall prevention

Parent/caregiver self care & rest

Run Chart Depicting Newborn Length of Stay
January 2019-December 2021





71% of babies treated with medications → 11% of babies treated with medications

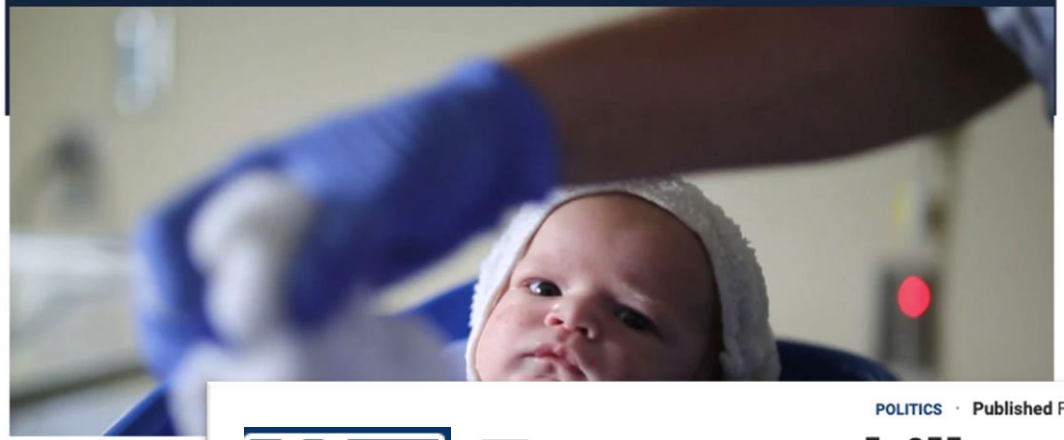
Other neonatal and infant outcomes

- Torticollis
  - Postural positioning when head twisted and turned to one side
  - Increased incidence in NAS (0.3-1.9% vs **11.1%**)
  - May result from hypertonicity, swaddling, increased time in bed
- Strabismus
  - Misalignment of the eyes
  - Concern for future stereoblindness, cosmesis, and self-image

1. McAllister JM, Hall ES, Hertenstein GER, Merhar SL, Uebel PL, Wexelblatt SL. Torticollis in Infants with a History of Neonatal Abstinence Syndrome. J Pediatr. 2018 May;196:305-308.
2. Rees P, Stilwell PA, Bolton C, Akillioglu M, Carter B, Gale C, Sutcliffe A. Childhood Health and Educational Outcomes After Neonatal Abstinence Syndrome: A Systematic Review and Meta-analysis. J Pediatr. 2020 Nov;226:149-156.e16.

Born Addicted: The Number of Opioid-Addicted Babies Is Soaring

East Tennessee counties are suing the makers of prescription drugs on behalf of thousands of infants born addicted to opioids.



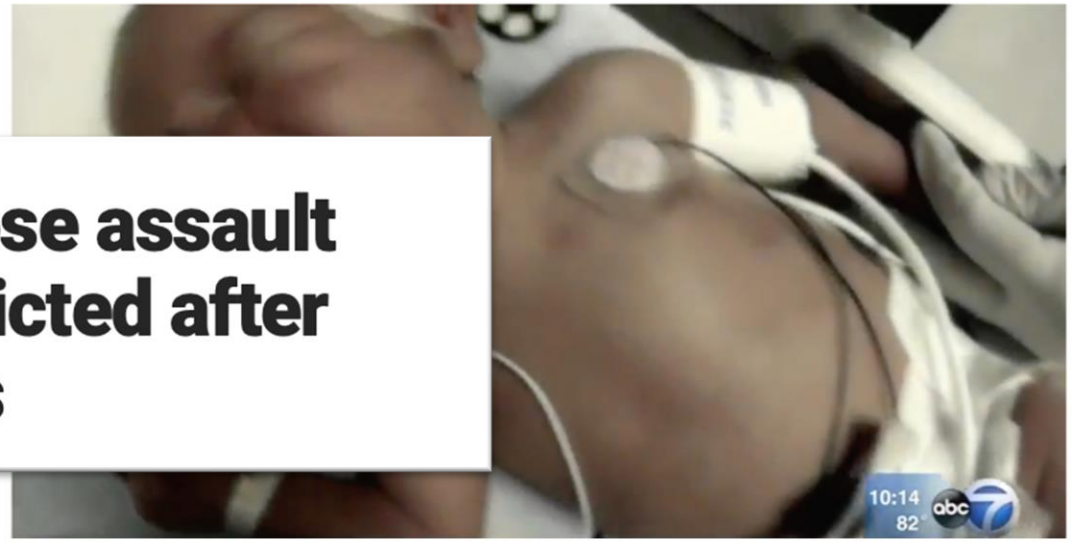
"His suffering is obvious. Born dependent on opiates, the month-old boy and thousands like him are the smallest victims of the opioid epidemic."

As opioid epidemic grows, so does number of babies born addicted

An ABC7 I-Team Investigation

By Chuck Goudie and Christine Tressel via

Tuesday, August 8, 2017



POLITICS · **Published** February 12, 2019 9:54pm EST

FOX NEWS channel

Tennessee bill would impose assault charges if baby's born addicted after mom uses drugs

PREGNANCY · **Published** September 27, 2016 7:06am EDT

More US babies born addicted to opiates like heroin

"COLUMBUS, Ohio — Baby M arrived in our neonatal intensive care unit the other day. Barely 24 hours old, she was clearly in pain."

"They can't "just say no" because they are babies born hooked, in a birth fight because of their mothers' addiction."

Long-term concerns

- What has been reported:
  - Developmental delay, behavior concerns, ADHD, lower IQ, poor academic testing
- What the research really says:
  - No data supports negative short-term (3 years) neurodevelopmental effects
  - Inconsistent data on long-term neurodevelopmental outcomes
- What exposure is really being described?
  - Parental mood disorders, trauma history, polysubstance use, parenting practices, inadequate nutrition, health care access, and other social determinants of health.
- Focus on family and surrounding components- providing resource, showcase strengths, support care, etc to mitigate risks.

1- Kaltenbach K, O'Grady KE, Heil SH, et al. Prenatal exposure to methadone or buprenorphine: early childhood developmental outcomes. Drug AlcoholDepend2018;185:40–49
2- Jones HE, Kaltenbach K, Benjamin T, Wachman EM, O'Grady KE. Prenatal Opioid Exposure, Neonatal Abstinence Syndrome/Neonatal Opioid Withdrawal Syndrome, and Later Child Development Research: Shortcomings and Solutions. J Addict Med. 2019 Mar/Apr;13(2):90-92.

Pregnancy Outcomes (Consequences of Discrimination)

- Difficulty in access to prenatal care
- Suboptimal prenatal care
- Increase risk of not breastfeeding
- Discontinuation of treatment for OUD
- *Worsened health care delivery and treatment outcomes*
- Death

1-Frazer Z, McConnell K, Jansson LM. Treatment for substance use disorders in pregnant women: Motivators and barriers. Drug Alcohol Depend. 2019 Dec 1;205:107652. doi: 10.1016/j.drugalcdep.2019.107652. Epub 2019 Oct 22. PMID: 31704383.

Thank you

USF Health
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