Opioid Use Disorder During Pregnancy:
The Role of Naltrexone in Decreasing Rates of Neonatal Abstinence Syndrome

Marissa Kanestrin, PA-S
Stony Brook University Physician Assistant Program

Stony Brook School of Health Technology and Management

Background

Opioid use disorder (OUD) during pregnancy has been linked with serious negative health outcomes for pregnant women and neonates, including preterm birth, stillbirth, maternal mortality, and neonatal abstinence syndrome (NAS).

What is NAS?

- Neonatal withdrawal from opioids or other substances that the neonate was exposed to in utero.
- Symptoms commonly include neonatal irritability, temperature dysregulation, poor feeding, failure to thrive, and in some cases seizures.
- Affected neonates may show signs and symptoms of withdrawal for up to 10 weeks and are often admitted to the NICU for prolonged periods of time.

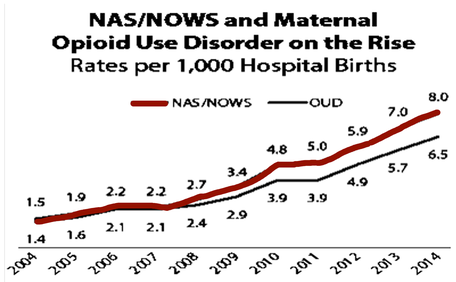

Figure 1: The CDC reported that OUD has risen more than 4 times among pregnant women and 4 times as many infants were born with NAS in 2014 than in 1999.

Opioid Use Disorder Treatment Options

Medication Assisted Treatment (MAT)

Prevents cravings, but patient maintains opioid dependence.
Methadone
Agonist at the mu-opioid receptor.
Buprenorphine
Mixed opioid receptor agonist-antagonist.

Medication Assisted Withdrawal (MAW)

Prevents cravings and does not produce dependence.
Naltrexone
Opioid antagonist. *5-7-day opioid free period before start.

Rationale

- MAT is the current standard of care for pregnant women, yet it is associated with the poor neonatal outcomes observed in neonates exposed to illicit opioids.
- Naltrexone is the third treatment option for nonpregnant patients with OUD, yet it is minimally offered as an option for pregnant patients due to insufficient research, risk of relapse and fear of maternal withdrawal.
- This research will help to identify whether NAS is entirely linked to action of opioid agonists.
- Women with OUD may become pregnant while being treated on naltrexone and therefore its effect on pregnancy and neonatal outcomes must be explored.
- Due to its mechanism of action, naltrexone will likely lead to decreased rates of NAS when compared to MAT.

PICO

In opioid dependent pregnant women, does medically assisted withdrawal with naltrexone result in reduced incidence of neonatal abstinence syndrome and better birth outcomes in comparison to the standard medication assisted treatment with methadone or buprenorphine?

Summary of Results

Birth Outcomes

- Naltrexone exposed neonates were significantly larger in birth weight, length and head circumference than methadone exposed neonates, but were not significantly different from buprenorphine exposed neonates in these categories.
- Mean gestational age at birth, mean birthweight or birthweight less than the 10th percentile were not significantly different between the MAT and naltrexone groups.

	Methadone			Buprenorphine			Naltrexone		
	Kelty	Wachman	Towers	Kelty	Wachman	Towers	Kelty	Wachman	Towers
Birth Weight (g)	2884.1 ± 658*	N/A	2901 ± 474	3035.8 ± 594	3047 ± 455	2901 ± 474	3137.1 ± 629	3263 ± 360	2976 ± 464
Head Circ. (cm)	33.1 ± 2.7*	N/A	33.06 ± 1.8*	33.6 ± 3.0	33.1 ± 1.7	33.06 ± 1.8*	33.9 ± 2.5	33.5 ± 1.7	33.52 ± 1.6
Gestational Age (wk)	37.7 ± 3.0	N/A	38.0 ± 2.1	38.1 ± 2.6	39.3 ± 1.4	38.0 ± 2.1	38.0 ± 2.5	39.1 ± 1.3	39.9 ± 1.8

*Figure 2: * = p<0.05; Cross-study comparison of birth outcomes in neonates exposed to naltrexone in utero compared with neonates exposed to methadone or buprenorphine.*

NAS and Length of Hospital Stay

- The rates of NAS in naltrexone exposed neonates proved to be lower in all the three studies.
- There was a significantly lower rate of neonatal intensive care unit admission and a significantly shorter length of neonatal hospital stay in naltrexone exposed neonates compared to MAT exposed neonates.

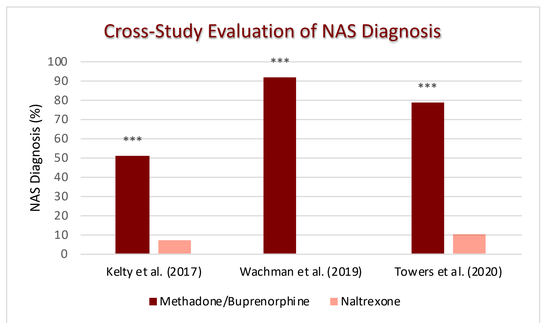

*Figure 3: *** = p<0.001*
Kelty et al. the NAS rate was significantly lower in the naltrexone group than MAT group (5/68 [7.5%] vs 154/323 [46.65%];P<0.001)
Wachman et al. the NAS rate was significantly lower in the naltrexone group than MAT group (0/6 [0%] vs 12/13 [92%];P<0.001)
Towers et al. the NAS rate was significantly lower in the naltrexone group than MAT group (10/119 [8.4%] vs 79/105[75.2%];P<0.001)

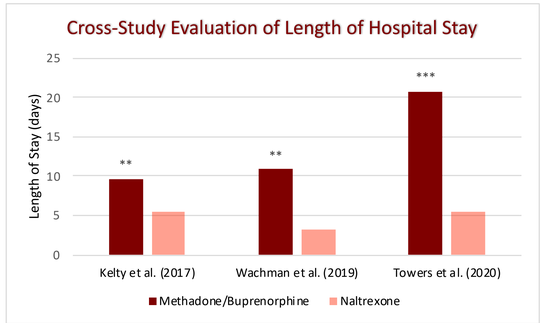

*Figure 4: *** = p<0.001, ** = p<0.01*
Kelty et al. the length of hospital stay was significantly lower in the naltrexone group than MAT group (5.5 days vs 9.65 days;P<0.01)
Wachman et al. the length of stay was significantly lower in the naltrexone group than MAT group (3.2 days vs 10.9 days;P<0.001)
Towers et al. the length of stay was significantly lower in the naltrexone group than MAT group (5.5 days vs 20.8 days;P<0.001)

Limitations

- **Sample size and study type.** The clinical use of naltrexone during pregnancy is in its infancy and therefore the research is limited to case studies and prospective and retrospective studies. Due to this, cohorts were relatively small and came from single centers. This may have skewed, or biased results based on demographics in the area.
- **Randomization.** Forcing an individual to alter her medication use based on a randomization arm would be unethical.
- **Provider Reluctance.** Providers practice evidence-based medicine. MAT has been the standard of care for pregnant women with OUD for over 50 years with good overall outcomes for mother and child. There is minimal evidence for use of naltrexone for pregnant women with OUD.
- Of note: Kelty et al. did not control for the concurrent use of other drugs of addiction. Therefore, NAS in the naltrexone exposed neonates may have been a result of other drugs that the mother was taking during gestation as it is a diagnosis of general withdrawal, not just opioid withdrawal.

Conclusion and Future Directions

- Overall, these results suggest that if a mother is willing to endure the symptoms of withdrawal for a five-to-seven-day period, **naltrexone may lead to lower rates of NAS and better birth outcomes** in comparison to opioid agonist treatment.
- Due to the size of the studies and the lack of diversity the **research is not yet viable enough to suggest naltrexone as a first line treatment for pregnant women**, however its safety for both the mother and the neonate is promising.

Future Directions

- More information is needed on the long-term effects of withdrawal during gestation as a result of the naltrexone treatment.
- Future research would benefit from a randomized, multicenter study in order to diversify patient populations as well as long-term following of the neonate in order to evaluate for later effects of the gestational naltrexone.
- Future studies should also exclude multi drug users in order to make an accurate conclusion on the rates of NAS in naltrexone exposed neonates.

Figure 5: CDC: Strategies for addressing OUD in the Pregnant Woman.

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