

Prenatal Opioid Exposure - Pediatric Grand Rounds-8-22-2025-Meeting Recording

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Kamat, Deepak M 0:40

Good morning and welcome to Pediatric Grand Rounds. It's 7:30 in San Antonio and time to start Pediatric Grand Rounds. It my it's my great pleasure and honor to introduce this morning's Grand Rounds speaker, Doctor Stephanie Marhar, who's a neonatologist at Cincinnati Children's Hospital Medical Center.

Research Director for NIC Follow-up Clinic and Professor of Pediatrics at the University of Cincinnati School of Medicine. Her research focuses on the impact of brain cells to the developing brain, particularly prenatal substance exposure on brain development and later neurodevelopment.

She's a Cincinnati Site Principal Investigator for NICHD Neonatal Research Network, the Outcomes of Babies with Opioid Exposure Study and the Healthy Brain and Child Development Study, and was one of the leaders of the multi.

Cite Eat Sleep Console Study that was published in New England Journal in 2023.

Doctor Malhar, thank you very much for accepting our invitation. The floor is yours.



Merhar, Stephanie 1:48

Well, morning, everybody, and thank you so much for having me. I'm happy to talk to you today about some of the things we've been doing in the past few years, trying to improve care for babies with prenatal opioid exposure.

See, now it's not wanting to. There we go. OK, so we'll kind of weave A. case presentation through this in the interest of of you know what what this actually might look like when you're caring for A. baby. So you're attending the delivery of A. 39 week baby due to meconium stained amniotic fluid.

The baby's mother initially took illicit opioids, mostly fentanyl, but after she found out she was pregnant at about 10 weeks, she started on daily methadone and took it throughout the rest of the pregnancy at delivery. Other than meconium staining of the cord, the baby looks well.

Her birth weight is 5.7 oz, 2466 grams, which is less than A. third percentile. Her

AFCARS are 9 to 9 and she stays with mom in the room.

So some of the questions we'll consider throughout this presentation is how should she be managed in the 1st 24 to 48 hours of life? What signs of withdrawal should we be looking for? What can we tell the family about the effects of prenatal methadone exposure on later development and behavior? And how should this baby be followed after hospital discharge?

So for this talk, first we'll talk about the Eat, Sleep, Console care tool for NOWS and the recently published ESC trial. And we'll talk about how prenatal opioid exposure affects the brain and neurodevelopment in the fetus, newborn and child. And finally, we'll talk about the recommended follow-up for opioid exposed to infants and children.

So this is A. slide that I present when I'm talking to local people because this is our opioid exposure rate per thousand live births in our area. We're at the the Cincinnati is is right between Ohio, Kentucky and Indiana all of which.

Which are states with high opioid exposure. But you can see here that this is this is based on billing data for all the birth hospitals we cover. Our our group covers all the birth hospitals in our area. So we have access to the billing data and so this is.

This is based on maternal universal urine toxicology, which happens at all our hospitals. So we have A. pretty good pulse on exactly how many babies are exposed to opioids based on mom's tox screen at the time of delivery. And so you can see that it kind of right around that 2014 mark when everybody started talking about. We had really high rates. It plateaued there for A. while and right before COVID, it decreased and has kind of come back to A. lower plateau. And I don't have the 24 and 25 data yet, but it's it's similar. And so I did take A. look at Texas. You guys are lower than the national average for newborn hospitalizations with babies with now. So probably about 1/3 of what we are and it looks, it looks like you guys had about 1000 babies treated for NAS in 2022, which are the the the most recent numbers that are available on the CDC website.

But that's, you know, that's only the babies who are actually treated versus those who are exposed. Those that number is going to be A. lot higher. So what this means is, is at the peak of the opioid epidemic, approximately 40,000 infants were born exposed to opioids each year in the US, which means that one infant is born to exposed to opioids approximately every 20.

20 minutes.

All right, so on to the case presentation. So what is NAS? So we've kind of moved the

terminology from NAS or neonatal abstinence syndrome to NAS. That's what we're all calling it now. And as you know, it's characterized by behavioral dysregulation. It occurs within two to three days of birth for infants exposed chronically to.

Opioids in utero kind of depending on where where in the cycle of of moms taking the opioid the baby was born. And then the signs include altered sleep, high muscle tone, tremors, irritability.

Poor feeding or alternatively, excessive feeding, vomiting, diarrhea, sweating, and tachypnea.

And so treatment of NAS is we don't have A. diagnostic test for it. It's based on observation and clinical signs and non pharmacologic care is the first line. So skin to skin breastfeeding mom still taking opioids is not A. contraindication to breastfeeding nor is hepatitis C.

Protecting the baby's sleep. And then if if these non-pharm measures don't work, then we have to move on to pharmacologic treatment, which is small replacement doses of morphine, methadone or buprenorphine. Most hospitals across the country still use morphine. In Cincinnati we have moved to buprenorphine.

Gosh, maybe maybe about 10 years ago now is when we we first started using it and all our hospitals have moved towards it. We find we've published some of our data showing that it's it, it results in A. shorter length of stay than than methadone, which is what we were previously using.

So after treating with one of these medications, if if A. baby continues with severe withdrawal, you might need the addition of A. secondary medication like phenobarbital or clonidine.

And we assume it's probably not good for developing brains to get opioids in the neonatal period, but it's probably also not good for developing brains to go through extreme withdrawal. And for many, many years, the standard of care assessment for babies with NAS was the Finnegan Neonatal Abstinence Scoring Tool.

It's it's was developed in the 70s. It includes this kind of laundry list of 21 signs of withdrawal, and scores have dictated when opioid treatment is initiated and how it's titrated up or down. And for many years, clinicians have believed that it overestimates the need for medication.

It's also fairly subjective and moms hate it. One of the moms from our area would say one nurse would score A. baby, my baby for sneezing. Another wouldn't score him for sneezing. One would score him for A. poopy diaper, another wouldn't. So the question arise is is there A. better way to assess babies with NAS and

determine the need for pharmacology?

Logic treatment.

So Matt Grossman and his colleagues at Yale first proposed this idea of eat, sleep, console. And the goal was really to emphasize the functional components of withdrawal. Can A. baby eat? Can A. baby sleep? And can A. baby be consoled? It also optimizes supportive and non-pharmacologic interventions as first line and emphasizes education, support and empowerment of families in the care of.

Their inputs.

This is what the ESC Care tool looks like. This it took some getting used to when we first started, but A. yes is actually bad. So for example, the question is not can A. baby eat, but instead does A. baby have poor eating due to an S or no's? And so instead of the laundry list of items in the Finnegan, it's really.

Distilled down to these three essential functions of A. baby. But it's not just the ESC score in prioritizing eating, sleeping, and consoling. It's A. whole shift in the paradigm of how we treat these babies and families with encouraging parental involvement and standardizing non-pharmacologic care.

So the purpose of this talk is not to teach you how to use the ESC care tool. That training is pretty involved, but I did want to go over quickly what the three components are. So for EAT, it's does A. baby take more than 10 minutes to coordinate feeding or breastfeed less than 10 minutes or feed less than 10 MLs or another age appropriate duration or volume depending on how old the baby is? Thought to be due to NAUS or NAS? And then the question for sleep is does A. baby sleep less than an hour between feeds due to NAUS or NAS? And for console, the official question is does A. baby take more than 10 minutes to console or cannot stay consoled for at least 10 minutes due to NAUS or NAS?

And there's an additional question for the consoling How much support A. baby needs? Is A. baby able to console on their own? Are they able to console within 10 minutes with caregiver support? Or do they take more than 10 minutes to console or can't stay consoled for at least 10 minutes, despite everything the caregiver is doing? And so here's the list of non-pharmacologic interventions that are integrated into the ESC care tool. None of this is groundbreaking, but it's just the fact that at every assessment the nurse has to go through this list and think about them and see if any of these interventions could be optimized further for the baby.

And most hospitals use these before ESD. So again, not innovative, but they're just formalized and standardized in the ESD care approach. And so this is a list of

everything that's there on the care tool, things that we were talking about at the beginning about rooming in.

Parental presence, skin to skin, swaddling, breastfeeding if possible, sucking, quiet environment and protecting sleep.

And so this is, this is what the huddles are. And there's two different types. There's the formal parent or caregiver huddle, which if a baby gets a yes on anything for the care tool, one or more of those things, and the parent and the caregiver, the nurse is supposed to reach out to the parent or caregiver and talk about if there's any.

Anything else that can be done on that list of non-pharm care to to be optimized to help the baby. And then so I've had the next assessment, the baby still is it has at least one yes. Then the nurse will bring in the provider who could be the pediatrician, could be the nurse practitioner, could be the resident.

Or the neonatologist to to talk with the nurse and the parent or caregiver to see if there's anything else that can be done, and if not, is a time to start medication.

And so the initial QI initiative in New England was led by Bonnie Whalen at Dartmouth, and it showed promise with shorter length of stay and less opioid treatment for the ESC babies. But the New England sites tended to have lots of moms stable on medication for opioid use disorder. They were able to room in with their infants. They were able to breastfeed.

And many of those hospitals were able to move babies with Nows to the pediatric floor in private rooms rather than a NICU setting. So it was really unknown how the ESC care approach would fare when private rooms for moms or infants weren't available, or when there were a high proportion of babies born to moms using illicit substances and unable to breastfeed or room in.

So in order to test the ESC care approach across a diverse array of sites, 2 pediatric research networks teamed up using funding from the NIH HEAL initiative to create the ACT NOW collaborative. And so the the IDEA States Pediatric Clinical Trials Network or ISPCTN was established in 2018 includes 18 sites.

Many of which are rural, which overlap with areas of high prevalence of NALS and the NRN, of which Cincinnati Children's is a site and there's two sites in Texas as well, was established in 1986, has 15 sites, mostly urban, many of which do not have a high prevalence of NALS and so the sites that did in the.

NRN participated in this study and Texas actually did not because the prevalence of mouse was slow at the NRN sites.

So the objective of the ESC study was to compare the ESC care approach to usual

institutional care with the Finnegan. We started the study during COVID and enrolled the first patient in September 2020. And it's still amazing to me that we managed to pull this off because it's a very nursing heavy intervention and you all probably remember.

Remember what nursing the nursing shortages were like during COVID. So we were lucky to have people who were very committed to this and made it happen regardless. So we conducted the main part of the study from September 2020 to March 2022 at 26 sites across the country. We randomized sites to switch from The Finnegan to ESC at a randomly allocated time, and because the intervention was at the site level and not the individual level, we were able to enroll all eligible infants at each site under waiver of consent. We did get consent for the long-term follow-up portion of the study, which I'll talk about.

So this is what the study design look like. All sites started with usual Karathofinigan in the light blue and then each of the 26 sites was put into one of these eight blocks. There are usually about 3 sites in each block and those sites got trained together on the ESC care approach.

And then during the transition period, site champions at each of the sites were trained and then went back and trained all of the nurses at their site in the ESC care approach and then switched to using ESC for every baby. We didn't collect data during the transition period, only during the usual care and ESC.

Periods. So the study was published in New England Journal in 2023 and we enrolled 1305 infants, 702 in the Finnegan group and 603 in the ESC group. And when we looked at the difference between groups, we found that infants managed with ESC had a length of hospital stay that was 7.8 days.

Versus 14 days in the Finnegan group and that 17.4% of the babies managed with ESC needed pharmacologic treatment versus 50% of the babies managed with the Finnegan. So based on this randomized trial, it seems to be good evidence that ESC should be the gold standard for management for babies with NELs.

There was some concern that we might treat too few babies with the ESC approach and have bad outcomes and readmissions and increased emergency room visits and even like non accidental trauma. So we did look at this. We did a we did a three-month chart review on all the babies in the study which included.

All the Uh visits, hospital readmissions and the critical safety outcomes of non-accidental trauma or death. The number of babies in either group with the non-accidental trauma or death was very low, but we did not see a difference in this

three-month composite safety outcome.

So when we first started this trial, there was concern that the ESC care approach would be kind of delaying treatment for babies who really needed it. And that would by the by the time we did treat them, that would end up leading to higher opioid doses, longer length of stay because they would have had more severe withdrawal before we actually treated them.

So we looked at this using a a secondary paper where we looked at only the pharmacologically treated infants in the study. So that was 463 of these 1305 babies. And we actually found the opposite of what people were worried about.

So we did find that the ESC group started treatment later, 75 hours versus 53 hours of life. Their mean total opioid exposure was lower. The ESC group had a shorter length of farm treatment, shorter length of hospital stay, and it wasn't statistically significant, but but.

Fewer babies were on adjuvant therapies like phenobarb or clonidine.

And this is another secondary paper. Because of the emphasis on keeping the maternal infant dyad together and treating fewer babies, we hypothesized that infants managed with ESC would breastfeed more. But there in there was some concern from the community that babies managed with ESC would have more weight loss because we were letting babies withdraw too much and.

And they were losing more weight because of the increased metabolic rate with withdrawal. So we looked at this and we did in fact find the proportion of breastfed infants was higher in the ESC group. More infants managed with ESC received exclusive breast milk, any breast milk and were directly breastfeeding at discharge. And there was no difference in the proportion of infants with weight loss, more than 10% of their birth weight or a difference in maximum percentage weight loss. The infants management ESC did have a lower weight Z score on day of like 3. But if you see there, I don't think this number is really clinically significant.

Interestingly though, when we added pharmacologic treatment into the model, the statistical model, the differences between the groups in breastfeeding outcomes disappeared. So this suggests that the increase in breastfeeding in the ESD group is mostly because we're not separating moms and babies by taking babies to the NICU for treatment for a prolonged period of time, because as we know it's.

It's hard to breastfeed in the NICU, especially when the baby is there for a week to 10 days.

So we also did a follow-up study in a in a subpopulation of of this infants in this

study. So we consented caregiver and infant dyads for long-term follow-up, which included three domains, infant Wellness, family and caregiver Wellness, and infant neurodevelopment and behavior. I'll talk about the third one today.

E.

So this is a longitudinal cohort study of infants enrolled in ESC. Same criteria. They were greater than or equal to 36 weeks at birth. We approached families for consent prior to hospital discharge, and the only additional criteria was that caregivers had to be able to speak and write English because we were doing a lot of questionnaires and about half of the caregivers of the overall study.

Consented to be part of the follow-up study and then it was all questionnaires until the two year visit, which was an in person visit with the Bailey Scales of Infant Development. And so we had 210 children in the usual care group, 218 in the ESC group who completed the Bailey.

So I'm kind of rushing through this because this is, this is unpublished data. First of all, we're we're working on getting this paper in and and I'm not kind of talking about all of the outcomes, but I did want to mention this because I think it's it's pretty interesting. So we looked at the demographic.

The traffic between the two groups, just like with the overall cohort, there were more infants in the usual care group that were from rural locations and more Hispanic infants. And that's just because of how the different sites switched over. The New Mexico sites switched over later, so they ended up having more babies in the usual care group, but otherwise the the groups were similar.

And I'm sure you all know what the Bailey is, but it's it is a comprehensive assessment of developmental functioning that we use as a major outcome for the Neonatal Research Network preemie studies. And it's just kind of the gold standard as far as looking at development at toddler age. So we did that.

That for the ESD study and it includes the three developmental domains of cognition, language and motor skills and the general population mean. The norms are at 100 with a standard deviation of 15.

So these are the results that we found. I know this is a busy slide, but so the on the left here is the well, the different pieces of the Bailey, again mean for the overall populations 100 with standard deviation of 15. So over here is the unadjusted analysis and to the right is the adjusted analysis.

Adjusted for sex and then all the things that were different between groups, gestational age, polysubstance exposure, and whether a baby went home with her

biological family from the NICU or from the hospital, the birth hospital, so.

The biggest thing to see from this study, well, well, first we found that there were differences that babies managed with ESC had higher motor composite, fine motor subscale and receptive language subscale.

Than babies managed with a Finnegan. And the other thing to notice is that across every one of these adjusted and unadjusted, that the ESC group had a trend towards higher scores for every one of these composites.

The other thing we looked at, we we looked at this in a categorical fashion. We wanted to see, you know, what, what difference does it make if a baby has a one point higher Bailey score? Not much, right? So we wanted to look at the the cutoffs as far as moderate or severe impairment down there in blue or mild impairment in the purplish color there.

So mild impairment is defined as one to two standard deviations below the population mean are a score of 84 to 70 to 84 and then moderate to severe impairment would be a score less than 70 on on any piece of the Bailey here. So we have again cognition, language and motor and you can see.

The general population should only have 13.6% of infants with mild impairment, and except for here with the ESC group having similar proportion of cognitive impairment, both groups had higher mild impairment than the general population, but the the ESC group had.

Lower proportion of mild infants with mild impairment than the usual care group for all three domains. And then for moderate to severe impairment, the rates of of impairment are much higher again than the general population in both groups, and there is no difference in moderate to severe impairment between the two groups.

So our conclusions for this were that infants with NAOS who are managed using the ESC care approach at higher Bailey scores at two years of age and a reduced risk of mild neurodevelopmental impairment when compared to those managed with usual care with the Finnegan. I didn't talk about the BITC. We also looked at a behavioral questionnaire. There was no difference between groups.

And then when compared to the general population, the study population had lower scores on the Bailey and a higher proportion at risk for behavioral problems. Again, data that I didn't talk about. So this is definitely an at risk population, but ESC appears to incrementally improve the outcomes at toddler age.

So why did this happen? Honestly, I was surprised. I was like there, this is really a safety outcome. We're just making sure that outcomes aren't worse. There's I did not

expect to see a better, better outcomes in the ESC group. So when we we thought about it, you know there's as we know there's more pharmacologic treatment and babies managed with the Finnegan postnatal opioid treatment.

Treatment could lead to worse neurodevelopment, although the studies that have been done, there's not a lot of them. Most of them show no difference in outcomes in babies who are exposed prenatally and treated versus exposed and not treated. And even though it's bad probably to to give opioids to a baby, that really isn't the. Treatment, the postnatal treatment for a couple days to a week versus the prenatal exposure of nine months. It seems like the prenatal exposure would be more important. So this kind of makes sense. There are a couple studies that show that that babies who were treated postnatally do have some more potential.

Disorders later on than exposed and untreated babies. So to to try to answer this question, we added pharmacologic treatment into the the statistical model. We still found that all scores were higher in the ESC group, although some of the formerly significant P values were now slightly more than .05, so it probably did.

It probably had something to do with it, the farm treatment piece. But what we like to think is that in the ESC care approach, it's really more about family empowerment, shared decision making, rooming in family support and and these things could improve parenting self-efficacy.

You know, decreased separation of moms and babies and increased breastfeeding. Any of those things could potentially play a role in improved neurodevelopment. So overall, for the ESC study, we found that infants managed with ESC had shorter lengths of hospital stay, were less likely to receive pharmacologic treatment, had no difference in safety outcomes throughout early infancy. If they did receive pharm treatment, they required less opioid. They were more likely to initiate and continue breastfeeding.

And they had higher scores on the motor, fine motor, receptive language subscales of the Bailey H2. So all of these things together provide strong evidence to support ESC as standard of care for infants with NALS.

So I'm not really gonna talk about implementation of ESC. I'm not sure what if there's if your units use it. It's hard when you don't have a lot of babies because it requires a significant amount of training for postpartum nurses and NICU nurses, lesser amount of training for for us and the ancillary staff, but it really does require a culture shift and some some creative.

Activity to allow moms to stay with babies. The hospital has to be on board. For

example, after a baby is moved to the NICU at some of our birth hospitals, we are still able to if unless labor and delivery or postpartum is super busy, we're able to to keep mom.

In a room, even though she's already been discharged and baby's not staying with her, she still has her own little hotel room that she so she can go over and be with the baby as much as possible. And same thing with getting meal meals for moms throughout the their whole, even if they're discharged throughout that whole process and the babies.

There and lots of volunteers, things like that to to hold the baby if if family is not able to be there. So our study team from the ESC study, we're working on getting these training and implementation materials posted for public access. There might be a partnership with Vaughn.

But you know, this is an NIH funded study and so really we should, we should be able to get these materials to everybody. So more to come on that.

All right, so moving on to this case presentation again, the baby in our case was managed with the ESC care approach. She stayed in mom's room for 96 hours and then mom was able to stay as a boarder after her own discharge. Baby had several yeses for consoling and sleep, but she didn't need to go to the NICU or be started on.

Medication. We just continued the non-pharm measures and we did get results in mom's urine tox screen and baby's umbilical cord. They were positive both for methadone only.

This mom just tried breastfeeding, but she decided it wasn't for her. So baby was started on 20 Cal Similac. She lost 12% of her birth weight, so we switched her to 24 Cal Sim and then she ended up going home with mom at 96 hours of life.

So probably families in the birth hospital are not going to be asking about the effects of prenatal methadone exposure on later development and behavior. But sometimes, you know, foster adoptive families are asking those questions and and and I think our OBS should potentially be talking about these things with with moms.

Prenatally as well. So the answer to that question is it's it's complicated. There's so many factors other than opioid exposure that could affect outcomes for these babies and children. And we really need to keep all of those factors in mind for any of the research that we do on this topic.

So this is a graphic that we made for a a review article that we published recently. So the things prenatally that could affect outcomes in addition to opioid exposure are

mom's nutrition, other exposures such as nicotine or alcohol, maternal toxic stress, maternal trauma, and then which opioid mom.

Is taking during pregnancy and how much in the neonatal period, whether a baby needs farm treatment, how severe their withdrawal is, whether they're breastfeeding later on in infancy, what the parent's mental health looks like, what the parenting style looks like, and if the baby is has one continuous primary caregiver.

That they're attached to versus being moved between different foster homes or different, you know, relatives, which sometimes happens. And then for the child overall, there's definitely genetic and epigenetic factors that predispose to opioid exposure that also might predispose to other behavioral and developmental things, adverse childhood experiences in a child's life, educational, daycare experiences, and of course, social determinants of health.

That said, I'm going to go through some of the research that has been done and that we've done on on these these children. So this is from a meta-analysis in 2021 looking at overall how opioid exposure affects the fetus, so.

There's a higher risk of stillbirth, a higher risk of perinatal death, and a higher risk of prematurity. The gestational age curve is shifted to the left to lower gestational ages, and then the risk of of preterm birth less than 37 weeks is higher and and babies who have been exposed to opioids prenatally and.

Even accounting for birth weight or accounting for gestational age, birth weight is lower. They have lower birth weight in general, higher risk of being small for gestational age, less than the 10th percentile.

And so we looked at, we wanted to look at the fetal brain because nobody had ever looked at this. So we recruited 65 women in the third trimester of pregnancy to undergo fetal MRI. It was 20 women who were taking opioids during pregnancy, most mostly moms who were stable on buprenorphine and methadone or methadone, and then 37 mothers who were unexpected.

Exposed to opioids and the mean gestational age at the time of fetal MRI was about 32 weeks. And I partnered with one of our neuroradiologists, Usha Nagaraj, to do this study. And so Usha and another colleague looked at biometric measurements of the fetal brain. They were masked to clinical information and they did the.

these measurements. You can see here, this is the transverse cerebellar diameter, but they did these measurements for 14 different areas in the fetal brain. And we found that seven of the 14 measurements they did were smaller in the opioid-exposed fetuses than unexposed fetuses. And this is after adjustment for gestational age.

Age at the time of MRI, fetal sex and also nicotine exposure. We know that smoking can also affect birth weight and and size and and even after adjustment for that, the babies with opioid exposure had smaller measurements of their brains.

Now on to the newborn. And so I'm sure you have all heard of punctate white matter lesions, which have been described a lot in preterm infants, but also in infants with congenital heart disease, infants with HIE and infants post-surgery. They're either small necroses, glial scars or micro hemorrhages.

It's hard to distinguish on MRI which one looking at, but it is thought to be mostly white matter injury and they are associated with abnormalities and white matter microstructure in preterm infants. And if you look at preterm infants later on, these punctate white matter lesions are associated with adverse motor and cognitive outcomes.

Later. So this is just an illustration of what they look like you. I'm not sure if you can see that there, but just the arrows are pointing to the the small punctate white matter lesions in this child. So first we looked at this pilot study of 20 opioid exposed infants and 20 controls. We did MRI's at 4 to 8 weeks of age.

And this was not an initial. We were not didn't expect to find this. We didn't. We didn't anticipate this at all because nothing had been published on this. But my partner radiologist would read, look at all these MRI to make sure there was nothing big that I needed to tell the families about. And I noticed that all of her reads coming back to me.

Where we're talking about these punctate white matter lesions and in the exposed infants in particular. And so we formally looked at it and it turned out that 40% of the exposed infants and none of the controls had these punctate white matter lesions on these MRI's.

But the exposed infants were more likely to have nicotine exposure and perinatal hepatitis C exposure. So was this really a thing or or was this just, you know, some random coincidence for these kids? But we felt like there might be something here to look at further. So based on the findings from our pilot studies in these.

Babies, not only the punctate white matter lesions, but some of the other volumes things we were seeing, we were able to secure NIH funding for the outcomes of babies with opioid exposure or Obo study. So this study has now it's still going on. We're still finishing up our two year, two year visits. I actually have a kid to see today after after I'm done with this.

We recruited 200 opioid exposed infants and 100 controls at at four sites, and we

oversampled the controls for babies with lower SES and increased nicotine exposure. Controls were not allowed to have any illicit drugs during pregnancy, including THC. We did MRI right after birth at six months and at 24 months of age, which we've been, you know, it's it's harder than one might think, easier than one might think to do an MRI on a to an unsedated 2 year old. I I thought there was no way we'd be getting any of them, but if you get them in a good nap or or right at bedtime, sometimes you can you can manage to get the MRI on them.

We did the neurobehavioral assessment, the ends at the zero to one month visit. At 12 months we did something called the home, which is a standardized, validated questionnaire or observation about the home environment and also the DAISY, which is a developmental assessment. And then at at age 2, we're also doing the Bailey.

And various other things. We collected all the umbilical cords for the children in the study. We did a chart review to look at their their NICU or hospital initial hospital stay. We actually did IQ testing on their primary caregiver and a bunch of surveys throughout the first two years of life.

So the first thing we looked at were these punctate white matter lesions in this cohort. So 165 exposed babies and 94 controls had MRI's that were able to be read for this and the majority had none of both groups. And we saw more in the control group than we did in in our initial pilot study. So 27%.

The exposed newborns had one or more punctate white matter lesions compared to 13% of the unexposed infants, and the adjusted odds ratio of having punctate white matter lesions if you were exposed was 3.56.

In this study, we also were able to look at the type of opioid exposure prenatally, and we found that opioid-exposed infants whose moms use methadone only were more likely to have punctate white matter lesions than infants whose mothers use buprenorphine. We do know that buprenorphine is associated with less growth restriction and fewer withdrawal symptoms.

In babies than methadone, medications have differences in the mechanism of action. Buprenorphine's a partial mu opioid agonist. Methadone's a full mu opioid receptor agonist. We're not sure you know exactly why, but some findings from basic science show differences between the effects of these medications. I'll.

Talk about a little bit later because we've consistently seen differences.

The next thing we looked at using the same cohort from the OBO study were regional brain volumes. This involved taking the MRI S that we had in the first month

of life, feeding these MRI S through a pipeline that automatically segments the brains into cortical Gray matter, white matter, deep Gray matter, cerebellum, brain stem, amygdala and hippocampus.

And it shows what a segmented brain looks like there. And what we found was after adjustment for postmenstrual age MRI, sex, birth weight and smoking, the opioid exposed group showed significantly smaller brain volumes in almost all areas. This included both overall brain volume at the bottom there.

But brain volumes in every area we looked at except for the hippocampus, which is a very small area. So since we adjusted for birth weight, it really does seem like these babies have disproportionately smaller brains, not just they're not just smaller overall. We did the same analysis looking at head circumference.

Instead of birth weight to see if, well, maybe they're, you know, their heads are just smaller and that's why. But we found the same thing. So it's it's not just that they're overall smaller, it's that their brains are disproportionately small.

In the same study, we then looked at the difference between opioid exposure type again. So methadone, buprenorphine or other opioids and unexposed babies. The other opioids included oxycodone, dilaudid, morphine, fentanyl and heroin.

And we after adjustment for these same things, we found differences in the areas that were affected depending on the type of opioid exposure. So methadone had a bigger effect on the white matter, which makes sense. We saw those increased punctate white matter lesions in the methadone exposed babies too and it seemed like buprenorphine had a bigger effect on the amygdala which.

Because you know the the part of the limbic system and important in addiction. So not quite sure what these findings mean yet, but interesting nonetheless.

And so these differences that we're seeing between buprenorphine and methadone, why are we seeing these things? So we looked at the basic science literature to see if that could help us kind of figure this out. And a couple, a couple studies have looked at this, a study looking at human cortical organoids, so basically human brains.

In the lab, they they looked at growth after exposing them to methadone or buprenorphine, and the growth was restricted in these organoids with methadone, but not with buprenorphine. Another group did a rat study where they looked at exposure to methadone or buprenorphine prenatally.

And it seems like the of the rat of the fetal rat saw more of the methadone than those exposed to buprenorphine. So the fetal brain concentration of methadone in the rats was what the maternal brain was, whereas the fetal brain concentration of

buprenorphine was only a third of what the maternal brain was seeing. So maybe they're just exposed to more.

Or opioids, if they're if mom is taking methadone. And then Lauren Jancy, who's one of the premier basic science researchers in this area. She has done a lot of work looking at methadone and and has seen a lot of systemic inflammatory responses. In the methadone exposed rats, which which we know from preemies that that inflammation definitely effects white matter development.

So we are we also looked at structural connectivity. This is actually not data from the Obo study. This is from a group in Scotland, but they looked at this is another way to look at white matter in the brain, which is is diffusion tensor imaging. They're looking at the tracks.

Of of white matter and they looked at 20 methadone exposed and 20 controls and looked at fractional anisotropy using diffusion tensor imaging. And they did find differences in the methadone exposed versus the control group. And then we looked at the same thing in the OBO cohort we also found.

Differences in the white matter microstructure between the unexposed and and exposed neonates. The areas in red are where we saw significant group differences in the white matter. And this is overall. We presented this at PAS last year. We haven't yet tried to look at methadone versus buprenorphine, but that paper is in preparation.

And then finally, I wanted to talk about functional connectivity, which is when we have the baby sleeping in the scanner, we're indirectly using brain blood flow, looking at the coordinated neuronal activity between different regions of the brain. And we found that connections involving the limbic system, which as you may remember is the emotional nervous system, also strongly implicated in addiction. Those connections were increased in the exposed infants versus the controls. So functionally there seems to be something going on as well.

And So what about the preterm brain? This is my colleague Nehal Parikh. He has a big cohort of of preemies who were all born less than 33 weeks and had brain MRI at term equivalent age and then were followed up to age 2. So just out of happenstance, there were some babies in that cohort that were had.

Prenatal opioid exposure 35 of the infants. And so we looked at that and we found that in these preemies infants exposed to opioids had rates of severe punctate white matter lesions as compared to the unexposed preemies. The opioid exposed toddlers also had lower scores on the Bailey motor composite, but no difference in the

diagnosis of C.

CP or scores on Bailey language or cognitive composited at H2, so seems to hold in preemies as well that these opioids are affecting white matter development.

OK. On No More Brain MRI talk, we're going to talk about how opioid exposure affects the child and I'm going to go through this pretty quickly. So as I talked about earlier, there's so many things that can confound this. As you get further from birth, there's more things in the environment that can affect later outcomes.

A lot of these studies that have been done are pretty old. They didn't adequately control for confounders, and they also used a wide range of definitions of prenatal opioid exposure.

But just overall, it seems like Bailey scores at age 2 tend to be within the normal range, but lower than controls. And that goes along with what we saw with the with the ESC cohort. Studies have not found differences depending on the type of prenatal exposure, whether mom was exposed to methadone or buprenorphine, or whether children.

Received pharmacologic treatment for analysis, but the sample sizes for these are pretty and one study found that infants discharged on phenobarbital had lower Bailey cognitive and language scores of two. And is that does that mean that phenobarbital is bad or does that mean that babies who have challenges with with brain development are going to be the.

The ones who need phenobarbital in order to to treat their very severe withdrawal. Nobody knows the answer to that.

And so again, a lot of children did score less than 85 or more than one standard deviation below the mean on the Bailey language composite, just like we saw in the ESC cohort. And at preschool age, children with opioid exposure have lower scores on the self, which is a A.

A preschool language assessment that controls.

When you go on to school age, there are continue to be differences. So this this cohort from Christchurch, New Zealand who's Samantha Lee and Leanne Woodward, it is a cohort they followed from birth. It's all methadone exposed babies and controls and they follow them up until they publish up until nine years now and.

Are kind of serially looking at looking at development and behavior. So they found that the IQ was lower at age 4 and that exposed children were more likely to have learning or processing impairment and they had lower scores on all reading and mathematic.

Subtest of the Woodcock Johnson, which is a just a academic assessment, and this is after correcting for relevant covariates. Some studies that have looked at huge data sets of linked administrative and health data have shown that those exposed babies or children have an increased need for special education.

and lower standardized test scores throughout childhood.

For motor skills, the literature's mixed. There's not very many studies. It seems like motor scores are within normal range, but lower than controls, even up to a kindergarten age.

And behavioral and emotional difficulties is where the the biggest difference seems to be seen in the same Christchurch cohort of from New Zealand. Across all the time points they looked at, the exposed children had higher total difficulty scores than controls, and the difficulties increased from toddler age to school age.

We also looked at this in our opioid exposed clinic and found that 30% of the children seen had borderline or clinical scores, which indicate problematic behavior. So that's much higher than the general population.

There have been a couple meta-analyses that have looked at these and found that exposed children have higher parent rated attention problems and higher scores for internalizing and externalizing behavior behaviors and increased sensory processing problems as well.

So the one of the most interesting things I think is is vision because a lot of these, a lot of these things, the behavior, the even the IQ you can explain away from other things. But the vision to me seems like it is clear that there is is a direct effect of opioids cause you can't this has nothing to do with socioeconomic status, right? So there is an increased rate of nystagmus and strabismus in in opioid exposed children. And we also looked at this in our clinic and we found we do a vision screener starting at six months of age, the same one, you know that the spot out, that's the well challenged spot vision screener.

And we found that 33% of the kids fail their vision screen, which is much higher than the rate of failure in the general population. We also found that infants exposed to methadone were more likely to fail vision screen than those exposed to buprenorphine. So just more potential evidence that methadone's affecting affecting the brain and the visual system.

So this is just a graphic that we made again for a recent review article showing all the differences that have been found in the literature between opioid exposed and control infants and children. And finally, we're just going to talk for a few minutes

about.

How babies should be followed after they go home, given everything we've talked about that you know it does. Things do appear to affect the brain and later neurodevelopment. They're at higher risk for special education visual problems. What should we do after we send these babies home from the birth hospital?

So I can't tell you what to do. I can tell you what we do in Cincinnati and again it's we are lucky or unlucky to have a large population of opioid exposed babies here. So we are able to have a whole clinic that's that is folded into our NICU follow-up clinic that sees these children. So a way.

You know, we don't do too many things that are different than what we do to the premie, for the premie or the the medically complex population. So sites that have fewer, fewer babies could just potentially fold the kids into the NICU follow-up clinic.

So we try to schedule the first visit within two weeks of birth hospital discharge. Social worker sees them. Help Me Grow is our state early intervention program. As in the case we talked about sending that baby home on 24 calorie, we will evaluate.

The whole formula and caloric concentration, because a lot of times once they get over that initial withdrawal period, they become hyperphasic. They're taking 220 MLS per kilo per day and you definitely don't want them on 24 calorie anymore. So somebody needs to be taking a look at that soon after they go home. At the next visit we will do the general movements assessment, which is you know a.

A screening test for cerebral palsy or a predictor of later cerebral palsy. And we have found that at least in our population in clinic, they're at a higher risk than the general population for CP. But we also see, you know, a complex population. So that's probably, we don't know if that's true for all opioid exposed children.

We look for strabismus. We look for torticollis because these kids tend to be tight to see if they need to be seen by a physical therapist. We'll do hepatitis C RNA testing if mom had a viral load during pregnancy and then the next visit we'll do the first spot vision screener. If they miss their general movements assessment, we'll do the Hammersmith infant neurologic exam by a therapist.

To look at their tone and motor skills. We do a hearing test at 12 months and then at 18 months, of course, during all of these visits, we're seeing them, we're talking to the family, we're seeing what the concerns are, we're doing an exam. But these are just the kind of standardized things that we do as well. So we do a sensor.

Processing screen at 18 months and then we'll schedule the Bailey visit at. So they'll have a Bailey by one of our therapists and we'll do a full neurologic exam and we'll talk to the family about the Bailey, try to get them in any any anything that we didn't know about that shows up on the Bailey, we'll try to get them into therapies and then their last visit in our clinic is.

We do the child behavior checklist and then refer them to the next step clinic, which we're again lucky enough to have a psychologist in our developmental behavioral Pediatrics who's interested in this population, who leaves this clinic and she sees them right at early school age and she's a psychologist.

We have a developmental Pediatrician, speech and OT. They do extensive evaluations. They've really seen a lot of anxiety in this population, a lot of ADHD, and so they give family supports that they need and help with IEPs and then refer kids to therapies if needed.

So that was a lot of information in less than an hour, but overall what I would like you to take away from this is that ESC should now be the standard of care for neonatal management for newborns with prenatal opioid exposure.

Prenatal opioid exposure does to appear to affect brain development, and it seems like methadone may affect the brain more than buprenorphine. And although children with prenatal opioid exposure have lower scores on developmental and IQ testing, most score within the normal range.

But as kids get older, behavior, sensory processing, anxiety and ADHD are out of concern. And clearly we need more research, especially as these kids get older into school age. There's very little out there.

And so that is all I have for you. I'm more than happy to take any questions if anybody has any.



Kamat, Deepak M 51:13

Thank you Doctor Mahar for that fascinating update on prenatal opioid exposure. I have a question in the chat box by Doctor Perlman, wondering if you are if you compare the non breastfeeding infants as a subgroup before and after the transition to EAC.

Did they have the same benefit as a breastfeeding infants who get some treatment via OPS and maternal milk?

MS Merhar, Stephanie 51:38

Let me look at that question itself. Let me see here.

 **Kamat, Deepak M** 51:40

But sure.

MS Merhar, Stephanie 51:45

So no, we did not look at that, especially we didn't really have.

We didn't really have granular data, you know, by the day in this study, but the, you know, we used to really think that encourage breastfeeding because of that reason, because we thought, oh, the babies are going to be getting some opioids from mom.

And more recently, that's probably not true. Like the the the amount that is transferred in breast milk, just like in a lot of the other things that are we thought were transferred in breast milk that are really not, it's very minimal. So the the benefit from breastfeeding is really probably not because of the maternal opioids that they're getting from the milk.

Really, because of the skin to skin, the bonding, the the the closeness to mom, that's really the benefit.

 **Kamat, Deepak M** 52:36

Thank you. Any other questions, comments for Dr. Manal?

Here another question in the chat box. What? Yeah, good. Yeah.

MS Merhar, Stephanie 52:43

Yeah, I see that. Yeah. What gestational age are you starting ESC if babies are born prematurely? That's a good question. And the study we didn't, you know, it was 36 weeks and above. And it's it's hard because the preemies don't show the same signs of withdrawal as the older kids probably do more to the immaturity of their nervous system.

Versus them not actually having withdrawal, I would say that we here have used it down to about 34 weeks ish. And if you're if you're if you have a exposed baby prior to that then it it gets really messy because at what point are you? Well, they're not eating.

But are they not eating because they're, you know, withdrawing or because they're a preemie? So it's it, it does get a little messy and probably that's another area where we really should do more research because I we really don't know the answer to that. But practically here we we do it about 34 weeks.



Kamat, Deepak M 53:39

Thank you. Any other questions, comments for Dr. Maha?



Merhar, Stephanie 54:03

All right, well, if anybody thinks of anything, I'm happy to my I'm sure you guys have my e-mail. I'm happy to to talk over e-mail about about any of this stuff.



Kamat, Deepak M 54:15

OK. Thank you, Doctor. I really appreciate it. Thank you. Thank you all for attending this morning's Grand Rounds. Just a quick announcement that this was my last Grand Rounds as the chair of the Grand Rounds Planning Committee because I'm retiring at the end of the month and Doctor Ranch will be taken taking over the responsibility. Of course, I'll be helping with organizing the grand rounds. Thank you all and we'll see you at the staff meeting. Thank you.



Merhar, Stephanie 54:47

Thank you.



Kamat, Deepak M stopped transcription