TESTIMONY BEFORE THE UNITED STATES SENATE
U.S. SENATE COMMITTEE ON HEALTH, EDUCATION, LABOR AND PENSIONS

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Summary of Testimony:

The number of infants diagnosed with neonatal abstinence syndrome, a post-natal drug withdrawal syndrome that most commonly occurs after *in utero* exposure to opioids, grew nearly 7-fold from 2000 to 2014. By 2014, one infant was born every 15 minutes in the US with the syndrome. The rise of neonatal abstinence syndrome occurred with concurrent increases in opioid use and opioid use disorder among pregnant women. The 21st Century Cures Act, the Comprehensive Addiction and Recovery Act and the Protecting Our Infants Act moved forward important child health priorities addressing the opioid epidemic. These important pieces of legislation may benefit from additional action, funding and implementation efforts. In addition, Congress could consider several actions to improve outcomes for pregnant women and infants impacted by the opioid epidemic, focused on prevention, expansion of opioid use disorder treatment, improving care for opioid-exposed infants and improving outcomes after discharge by bolstering the child welfare system and early intervention systems.

Chairman Alexander, Ranking Member Murray and honorable members of the Committee, thank you for the opportunity to speak here today about the impact of the opioid epidemic on our nation's families. My name is Dr. Stephen Patrick, and I am a board-certified pediatrician and neonatologist at the Monroe Carell Jr. Children's Hospital at Vanderbilt. At Vanderbilt I direct a National Institutes of Health-funded research program focused on the effect that the opioid epidemic has had on pregnant women and infants. I have published extensively on this topic, including in *JAMA*, *Pediatrics*, *The New England Journal of Medicine* and *Health Affairs*. I also serve on the American Academy of Pediatrics Committee on Substance Use and Prevention and have previously served as an advisor to the White House Office of National Drug Control Policy.

Recently, I was caring for a sick infant at Vanderbilt who had been transferred to our neonatal intensive care unit from the newborn nursery. The infant had trouble feeding, was jittery and had rapid weight loss – more than ten percent of his body weight in a few days. Something was wrong.

The infant was exhibiting classic signs of neonatal abstinence syndrome, a post-natal drug withdrawal syndrome that most commonly occurs after *in utero* exposure to opioids, but like many conditions, neonatal abstinence syndrome can be difficult to diagnose in the newborn. Over the next few days, the infant was increasingly irritable, continued to have difficulty feeding, increased muscle tone and muscle jerking. We suspected opioid withdrawal, but his mother denied using any drugs. Despite this, we started treating the infant as we would any infant with the syndrome.

After a week in the hospital, the umbilical cord drug screen came back positive for an opioid. As I walked into the infant's room to talk to his mother I could sense her guilt and anxiety. She cried as I talked to her about the drug test, and wondered aloud if she would lose custody of her infant. She had been afraid of my response and the response from child welfare. Like too many women I see, she

became dependent on an opioid after an accident, was not able to get treatment for her opioid use disorder while pregnant and was too scared and ashamed to ask for help. This combination was dangerous to her and her infant.

Had I known this mother was using an opioid, I could have started treating the baby earlier by controlling the environment, making adjustments to the baby's care to make the withdrawal less severe while teaching his mother how to recognize and mange his symptoms. Perhaps more optimally, his mother could have already had access to comprehensive treatment during her pregnancy.

As a practicing neonatologist, I have seen first-hand the destructive impact of opioids on families. Neonatologists like me are trained to care for very premature infants and infants with severe birth defects. However, a few years ago we began to see an influx of a different type of infant – those having withdrawal from opioids, known as neonatal abstinence syndrome. These infants can be inconsolable, have muscle tremors, have trouble feeding, difficulty sleeping and breathing problems. Infants experiencing severe neonatal abstinence syndrome require treatment with an opioid like morphine or methadone, and stay in the hospital an average of more than three weeks.[1]

Once rare, this diagnosis has become increasingly common. Our team's research has found that from 2000 to 2014, the number of infants diagnosed with neonatal abstinence syndrome grew nearly 7-fold.[1-3] Put another way, nearly one infant is born every 15 minutes with signs of drug withdrawal in the US.[3i]

[i] Results embargoed, but permission to cite given by editor. Paper will appear online in the journal *Pediatrics* in March.

This rise in the incidence of neonatal abstinence syndrome happened in parallel with increases in opioid use nationally. In 2015, Americans were prescribed three times as many opioids as they were in 1999.[4] That year, more than 37 percent of American adults were prescribed at least one opioid pain reliever.[5] Research, including our own, has found similarly high rates of opioid prescribing in women of reproductive age[6] and pregnant women.[7] More recently, we have experienced a surge in use and complications due to heroin and fentanyl use. In 2016, more than 42,000 Americans died from an opioid overdose death[8] and some of them were pregnant or had recently been pregnant.

Implementation of Existing Legislation

I applaud the Committee and the Congress for the passage of the 21st Century Cures Act, the Comprehensive Addiction and Recovery Act and the Protecting Our Infants Act. Together, these pieces of legislation have moved forward important child health priorities for addressing the opioid epidemic. Even with the passage of these landmark pieces of legislation, there is an urgent need for additional legislative action and Executive Branch implementation of these laws. For example, there remains confusion at the state and provider level around some provisions of the Comprehensive Addiction and Recovery Act and, while SAMHSA has released its final report for the Protecting Our Infants Act, it is unclear how the recommendations contained in the report are being implemented.

Protecting Our Infants Act

The Protecting Our Infants Act was passed just after a Government Accountability Office (GAO) report highlighted large gaps in research and service delivery for mothers and infants impacted by opioid use.[9] The Act required that the Department of Health and Human Services (HHS) conduct a review of its planning and coordination of activities related to prenatal opioid use and neonatal abstinence syndrome. It also mandated that HHS study and develop recommendations for preventing prenatal opioid exposure, treating opioid use disorder among pregnant women, and preventing, identifying and treating neonatal abstinence syndrome and its consequences. Lastly, the Act required

HHS develop a strategy to address gaps in research, federal programs and coordination. Last year, SAMHSA released its final strategy focused on three domains: prevention, treatment and services. While these recommendations are important, it remains unclear how they will be implemented, funded and coordinated.

Comprehensive Addiction and Recovery Act & the Child Abuse Prevention and Treatment Act

The already-taxed child welfare system is being stretched even more thinly by the opioid epidemic. In 2015, the number of children entering foster care increased to nearly 270,000, up from 251,352 in 2012. In 2015, infants represented nearly one-fifth of all removals of children from their families to foster care, totaling 47,219. Parental substance use was a factor in the foster care placement in nearly one-third of all cases.[10]

Congress has a role in helping to improve collaboration among health care providers, the child welfare system and substance use disorder agencies in responding to the rise of substance use disorders among pregnant and parenting women and affected infants and those who experience neonatal abstinence syndrome. Your actions in 2016 to amend the Child Abuse Prevention and Treatment Act (CAPTA) in passing the Comprehensive Addiction and Recovery Act added important clarifications to the requirements for states to develop infant “plans of safe care” that also address the needs of the family or caregiver in instances when an infant is identified as affected by substance abuse, experiences withdrawal symptoms or fetal alcohol spectrum disorder. The goal of these plans is to engage child health and welfare professionals in collaborating to ensure the safety of these vulnerable infants upon discharge from the hospital.

Unfortunately, those requirements came without clear guidance or, importantly, sufficient resources for implementation. States need additional guidance, funds, and resources from the federal government to ensure infant safety and to keep families intact when appropriate. States and

communities need assistance to develop their key definitions and need funding for services to address these families' needs. I have experienced first-hand how these changes in statute are being interpreted with great variability among doctors, hospitals and child protective services. I would encourage the Committee to continue to exercise robust oversight of the federal agencies working with states on implementing and monitoring CAPTA, and to provide funding additional legislative clarity where needed.

In addition to the severe gap in funding the CAPTA-required plans of safe care, funds to ensure family-centered treatment are currently lacking. Congress should act to ensure that funds allocated across Medicaid, CAPTA, Title IV of child welfare services, and the Substance Abuse Prevention and Treatment Block Grant are flexible, but also targeted to prevent children from being removed from their family whenever possible. Removing children is itself a form of trauma and one that can often be avoided if we provide families with the treatment and services they need to stay safely together. Treatment programs for pregnant and parenting women funded under the block grant need expansion because the program has not changed in nearly 20 years.[11] It is time for Congress to revisit the funding mechanisms for these two-generation programs and encourage expansion of services for this population through Medicaid, the Block Grant, CAPTA and grants to pregnant and parenting women programs.

Recommendations

Addressing the complexity of perinatal opioid use and neonatal abstinence syndrome requires a thoughtful public health approach targeting the pre-pregnancy, pregnancy and post-pregnancy periods for women and infants. Our goal should be to promote healthy mothers and infants by supporting prevention and recovery:

My recommendations fall into three broad categories: improving care for mothers, improving infant outcomes, and research.

Improving Care for Mothers

Primary prevention of opioid use disorder begins with preventing unnecessary opioid use well before pregnancy. Non-medical use of opioids among adolescents commonly begins with opioids not prescribed to them, but rather to a family member or friend. Congress should take steps to decrease the opioid supply, including through responsible prescribing and drug takeback programs.

Too many health care providers are still unaware of the implication of their prescribing patterns for their patients. It is clear that additional provider education in this area is greatly needed. Congress should also bolster prescription drug monitoring programs[12] by providing states with additional resources to modernize them and integrate them better into physician work flow and electronic medical records.

Improving access to contraception, including long-acting reversible contraception, is vitally important because research suggests that women with opioid use disorder are nearly twice as likely to have an unplanned pregnancy.[13] Congress should protect and expand women's access to all forms of contraception approved by the U.S. Food and Drug Administration, including coverage of contraceptives without cost-sharing.

Congress should also act to expand access to opioid treatment programs, especially for pregnant women and postpartum. Untreated opioid use disorder among pregnant women leads to poor outcomes for the mother and infant;[14] however, treatment with opioid agonist therapies like buprenorphine and methadone are highly effective,[15] especially for pregnant women.[14] These therapies improve treatment retention,[16] reduce relapse risk,[16-19] reduce HIV-risk,[16,20] reduce criminal

behavior,[18] reduce risk of overdose death[21] and improve birth weight.[22] Despite evidence that treatment is effective in mitigating adverse outcomes from opioid use disorder, evidence suggests that the majority of women in need of treatment do not receive it.[23] Congress should work toward ensuring that treatment is available when it is needed, including opioid agonist therapies when appropriate, and it should be comprehensive, trauma-informed, gender-specific and inclusive of obstetric and pediatric care. Gender-specific treatment must include the ability of the mother to bring her children with her so that she is not faced with the unfair choice of getting treatment or caring for her children.

Congress should resist any efforts to pursue punitive measures against pregnant women using opioids as some state legislatures have done. Major medical associations, including both the American College of Obstetricians and Gynecologists[24] and the American Academy of Pediatrics,[25] endorse non-punitive approaches to opioid use in pregnancy. SAMHSA estimates that more than 400,000 infants every year are exposed to alcohol or illicit substances.[26] Punitive approaches are unethical, impractical and incentivize women to avoid care or not report their substance use to their provider. If a woman is fearful of criminal punishment, she may avoid prenatal care, go to another state to deliver, or even deliver at home, potentially resulting in adverse outcomes for mother and baby.[ii] Infants are routinely discharged at 24 to 48 hours of life, but signs of drug withdrawal may not develop until 72 hours of life or later.[27] If women are unwilling to disclose substance use, their infants are at risk of experiencing withdrawal at home with potentially dire health consequences including death.

[ii] http://www.wbir.com/article/news/local/mother-of-drug-dependent-baby-tells-her-story/51-63840991

Improving Infant Outcomes

Throughout the US, opioid-exposed infants experience variable treatment[28] resulting in variable outcomes.[29] State and national perinatal quality improvement groups and hospital teams like ours at Vanderbilt are working to decrease this variability, but Congress should act to accelerate this vital work. Medicaid in particular could play a key role in standardizing care and breaking down discontinuities in care from pregnancy through the post-natal period. Medicaid is financially responsible for 80% of infants diagnosed with neonatal abstinence syndrome.[2] Our team's research, due to be published next month, found that in 2014 neonatal abstinence syndrome accounted for 6.7% of all birth related expenditures for Medicaid nationally.[3][iii] In that study there was some evidence that infants in Medicaid are being treated differently than those with private insurance, with higher rates of transfer to another hospital and longer hospital stays for infants covered by Medicaid.[3] Medicaid programs are well-positioned to achieve the "triple aim" for families impacted by opioid use, by improving population health, improving the experience for pregnant women and infants and reducing cost.[30] Congress should urge the Centers for Medicare and Medicaid Services to play a more active role in working with state Medicaid programs to address care for substance-exposed infants, including those with neonatal abstinence syndrome.

Our nation has a long way to go to improve care for infants with neonatal abstinence syndrome, from better identification and treatment (including non-pharmacologic treatment) to improvements in the structure of care and minimizing separation of the maternal/infant dyad. Systems need to be agile, responding to new complications of the opioid-epidemic like hepatitis C. In a study conducted in partnership with the Tennessee Department of Health, my colleagues and I found that hepatitis C rates among pregnant women nearly doubled in the US from 2009 to 2014.[31] Some states were more affected than others, with the highest rates in West Virginia, where one in fifty infants was exposed to

[iii] Results embargoed, but permission to cite given by editor. Paper will appear online in the journal *Pediatrics* in March.

the virus in 2014. Exposed infants are completely asymptomatic and it is not possible to tell if they will acquire the virus until they are several months old. Screening for hepatitis C during pregnancy is not universal, and emerging data suggest that most exposed infants are not followed up to see if they become hepatitis C virus-positive.[32] Congress should support and fund Centers for Disease Control and Prevention efforts to better identify pregnant women with hepatitis C virus. Congress should also urge the Centers for Medicaid and Medicare Services to develop programs to ensure exposed infants are appropriately followed.

We also must do a better job of supporting families in the transition to home through initiatives like home visiting. The Maternal, Infant, and Early Childhood Home Visiting program provides funding to states to implement and expand effective home visiting programs that improve the early health, school readiness and economic stability of children and families. High-quality home visiting services to infants and young children can improve family relationships, advance school readiness, reduce child maltreatment, improve maternal-infant health outcomes, and increase family economic self-sufficiency.[33] However, funding for the program expired September 2017, and Congress has yet to renew this funding. Congress should renew funding for the program as quickly as possible at the current level of $400 million annually for five more years, so that this program can continue its successes at the local level for the most vulnerable children and families.

Next, the Individuals with Disabilities Education Act (IDEA) Part C supports early intervention services, like speech therapy, physical therapy and occupational therapy to infants with developmental delays. In 2004, reauthorization of this program extended to substance-exposed infants and infants having drug withdrawal after birth; however, adoption has been uneven. While as a provider I refer substance-exposed infants to early intervention services, it is not clear how many others are. Congress should ensure better linkages between child welfare, substance use disorder treatment for pregnant women and early intervention services.

Research

In 2015, the GAO highlighted research gaps and reasons for the difficulty of conducting research on prenatal substance use and neonatal abstinence syndrome.[9] As the GAO report noted, the federal government spent only $21.6 million over a seven-year period on research related to perinatal opioid use and neonatal abstinence syndrome – a small investment considering neonatal abstinence syndrome birth hospitalizations cost Medicaid $462 million in 2014.[3] The 21st Century Cures Act provided urgently-needed funding to states to support treatment and prevention, but an urgent need remains for additional National Institutes of Health funding specifically targeting the opioid epidemic. Congress should direct additional funding to the National Institute on Drug Abuse to expand research focused on improving outcomes pregnant women and infants impacted by the opioid epidemic.

Summary

The opioid epidemic is taking a terrible toll on pregnant women and infants. Congress must act to address the urgent need for additional resources and coordination. For women and infants, like the ones in my introduction, the current system is disjointed and does not consider the needs of the mother and infant together. Without treatment, pregnant women are at risk of overdose death. Discharging infants home to a safe environment could be achieved by a more proactive and better funded child welfare system.

Every day, people are dying, pregnant women are not getting the treatment they need and infants are spending their first days or weeks of life in drug withdrawal. In just the time we are meeting here, 8 infants will be born with neonatal abstinence syndrome and 10 people will die from an overdose. These are our brothers and sisters and our children – they need us, now perhaps more than ever.

Mr. Chairman, thank you for the opportunity to speak today. I look forward to your questions.

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A Public Health Response to Opioid Use in Pregnancy

Stephen W. Patrick, MD, MPH, MS, FAAP,[a,b,c,d,e] Davida M. Schiff, MD, FAAP,[f] COMMITTEE ON SUBSTANCE USE AND PREVENTION

The use of opioids during pregnancy has grown rapidly in the past decade. As opioid use during pregnancy increased, so did complications from their use, including neonatal abstinence syndrome. Several state governments responded to this increase by prosecuting and incarcerating pregnant women with substance use disorders; however, this approach has no proven benefits for maternal or infant health and may lead to avoidance of prenatal care and a decreased willingness to engage in substance use disorder treatment programs. A public health response, rather than a punitive approach to the opioid epidemic and substance use during pregnancy, is critical, including the following: a focus on preventing unintended pregnancies and improving access to contraception; universal screening for alcohol and other drug use in women of childbearing age; knowledge and informed consent of maternal drug testing and reporting practices; improved access to comprehensive obstetric care, including opioid-replacement therapy; gender-specific substance use treatment programs; and improved funding for social services and child welfare systems. The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool (December 2016).

INTRODUCTION

Substance use during pregnancy occurs commonly in the United States. In 2009, the Substance Abuse and Mental Health Administration estimated that 400 000 infants each year are exposed to alcohol or illicit drugs in utero.[1] Although concern regarding substance use in pregnancy is not new, it has recently increased among health care providers, the public, and policy makers as the opioid epidemic's impact reached an increasing portion of the US population, including pregnant women and their infants.[2,3] Several recent studies highlighted an increase in prescription opioid use among women of childbearing age[4] and among pregnant women.[5,6] As opioid use among pregnant women increased, the rate of infants in the United States experiencing opioid withdrawal after

abstract

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birth, known as neonatal abstinence syndrome (NAS), grew nearly fivefold over the past decade.[2,7] By 2012 in the United States, on average, 1 infant was born every 25 minutes experiencing signs of withdrawal, accounting for an estimated $1.5 billion in hospital charges.[2] The issues surrounding substance use in pregnancy are complex and merit a thoughtful public health response focused on prevention, expansion of treatment to women with substance use disorder, and improved funding for child welfare systems to improve the health of the substance-exposed mother-infant dyad.

Primary Prevention

A public health approach to substance use in pregnancy should begin with primary prevention: preventing substance and opioid misuse before pregnancy. In 2011, the White House Office of National Drug Control Policy released a plan to respond to the prescription opioid epidemic that has 4 main pillars: (1) improve public and provider education about the abuse potential of opioids, (2) reduce the abuse of prescription opioids by bolstering prescription drug monitoring programs, (3) ensure that unused opioids are properly disposed, and (4) provide law enforcement with the tools needed to stop illegal prescribing or dispensing of opioids.[8] Public health and policy approaches to the prescription opioid epidemic will help eliminate the burden of opioid use disorder before pregnancy begins.

Preconception and interconception (between pregnancies) care plays an important role in improving outcomes for pregnant women. Counseling during these crucial periods may play a role in identifying and mitigating risk to mothers and their infants.[9] Although 31% to 47% of US pregnancies are unintended, research suggests that, for women with opioid use disorder, the proportion of unintended pregnancies was higher than 85%.[10] Education and expansion of access to effective contraception, particularly long-acting reversible contraception (LARC) methods,[11] are important components of primary prevention. Access to LARC methods is supported by both the American Academy of Family Physicians (AAFP) and the American College of Obstetricians and Gynecologists (ACOG)[12,13] during both the pre- and interconception periods. However, there remain barriers to highly effective contraception in many states. For example, the ACOG supports placement of LARC devices during the immediate postpartum period to improve the use of LARC among postpartum women[13]; however, bundled payments for delivery create a relative financial disincentive to place LARC devices at the time of delivery. State Medicaid programs play a critical role in ensuring access to highly effective contraception at the time when it is desired, including the time of delivery. However, recent research suggests that states are variable in aligning financial incentives to ensure access to LARC methods if elected at the time of delivery.[14]

Improved Identification and Access to Treatment

The early identification of women who use illicit substances during pregnancy is vital to improving outcomes for both mothers and infants. Routine universal screening through brief questionnaires for drug, alcohol, and tobacco use before and throughout pregnancy is recommended by the ACOG and AAFP.[9,15,16] The ACOG recommends that screening consist of a mutual dialogue between clinician and patient and be performed in partnership with the woman with the use of validated screening tools,[17,18] with her consent, and screening should be applied equally to all women, regardless of their age, race, ethnicity, or socioeconomic status.[19]

The benefits of drug testing in addition to screening during pregnancy remain uncertain. Targeted urine drug-testing programs have been shown to disproportionately affect low-income women of racial or ethnic minorities,[20–23] prompting some to develop universal urine toxicology testing protocols at the time of delivery.[24] Although urine toxicology tests can provide objective evidence of drug use at 1 point in time, they do not enable providers to determine the frequency of use or to characterize the frequency or degree of use.[25,26] Studies comparing the difference between verbal screening and urine drug testing are mixed; 1 study found superior identification with verbal screening and another identified individuals with positive urine drug test results who were not previously known to have used opioids.[17,24] Consistent with ACOG policy, informed consent should occur at the time of drug testing and a woman should be informed how a positive test result will be used for both medical treatment and reporting to child welfare agencies.[19]

Drug screening and testing in pregnancy should be used to identify women with substance use disorder and enable access to comprehensive treatment. Access to comprehensive prenatal care and treatment of women with substance use disorders is associated with fewer preterm deliveries, small-for-gestational-age infants, and infants with low birth weight.[27–30] The literature suggests that pregnancy can motivate women with substance use disorders to seek treatment.[31] However, there remains a dearth of comprehensive treatment programs geared toward pregnant and parenting women. Only 19 states have treatment programs specifically designed for pregnant women.[32] Furthermore, only 15% of current treatment centers across

the country offer specific services for pregnant women with substance use disorders, and the majority of these are located in urban areas.[33] Women with substance use disorder report high rates of past trauma, including physical and sexual abuse, and need access to gender-specific, family-friendly addiction treatment programs, psychosocial services, and mental health treatment.[34–36] Trauma-informed services should be framed by an understanding of the effects of interpersonal violence and victimization of women with substance use disorders, with a focus on creating a strengths-based environment to foster resiliency and to minimize the possibility of retraumatization.[37] In addition, pregnant and parenting women are likely to remain in treatment if on-site child care and child services are provided and staff work to develop collaborative and nonjudgmental therapeutic alliances through the use of trauma-informed care approaches.[38,39] Positive outcomes of treatment in pregnant and parenting women who complete treatment programs include employment, less engagement in criminal activity, and lower risk of relapse.[40,41]

For women with opioid use disorder, the abrupt discontinuation of opioids in pregnancy can result in preterm labor, fetal distress, or fetal demise. Furthermore, medically supervised withdrawal from opioids in opioid-dependent women is currently not recommended during pregnancy, because the literature suggests that withdrawal is associated with high relapse rates.[16] Opioid agonist therapy, also known as medication-assisted treatment, with methadone or buprenorphine has emerged as the standard for pregnant women with opioid use disorder.[42] Opioid agonist therapy has been shown to be safe and effective in pregnancy[16,43,44] and is associated with improved maternal and infant outcomes.[45,46]

Knowledge of substance use during pregnancy is vital to the pediatrician's ability to effectively provide care for substance-exposed infants. For example, exposure to opioids in utero may lead to an infant developing NAS. The presentation of NAS may be delayed for several days depending on several factors (eg, timing of maternal drug use, drug type, infant metabolism),[47] and clinical signs of NAS can be vague (eg, irritability, poor feeding). Each of these factors creates the possibility that a diagnosis of NAS may be missed without the knowledge of opioid exposure, potentially leading to poor outcomes for infants.[47] Teamwork between all health care providers, including but not limited to obstetric, pediatric, family, and addiction medicine, is vital to optimal care of substance-exposed infants. When inadequate information about drug exposure exists, testing an infant's urine, meconium, or umbilical cord tissue can be important in ensuring the optimal care of the infant.

Criminal Justice Approaches to Substance Use in Pregnancy

In recent years, a number of state legislatures have passed new laws or applied existing child endangerment laws to prosecute pregnant women for illicit drug use during pregnancy.[32,48] The American Academy of Pediatrics (AAP) first published recommendations on substance-exposed infants in 1990 and reaffirmed its position in 1995 that "punitive measures taken toward pregnant women, such as criminal prosecution and incarceration, have no proven benefits for infant health" and argued that "the public must be assured of nonpunitive access to comprehensive care that meets the needs of the substance-abusing pregnant woman and her infant."[49,50]

More than 20 national organizations have since published statements against the prosecution and punishment of pregnant women who use illicit substances: these include the American Medical Association, the AAFP, the ACOG, the American Public Health Association, the American Nurses Association, the American Psychiatric Association, the National Perinatal Association, the American Society of Addiction Medicine, the March of Dimes, and the Association of Women's Health, Obstetric and Neonatal Nurses.[51–60] Despite the strong consensus from the medical and public health communities affirming that a punitive approach during pregnancy is ineffective and potentially harmful, there has been a recent increase in the number of states passing and considering criminal prosecution laws that selectively target pregnant women with substance use disorders.[61–63]

The existing literature supports the position that punitive approaches to substance use in pregnancy are ineffective and may have detrimental effects on both maternal and child health. Qualitative research performed in pregnant women with substance use disorders shows that women may avoid prenatal care for fear of being reported to the police and child protective services.[23,64–66] In addition, surveys of pregnant women found that punitive laws targeted at pregnant women who use drugs are a significant deterrent to obtaining regular prenatal care and agreeing to drug testing,[67] and women who deliver without receiving any prenatal care are more likely have a history of substance use.[68] For these reasons, the AAP supports an approach toward substance use in pregnancy that focuses on a public health approach of primary prevention, improving access to treatment, and promoting the provider-patient relationship rather than punitive measures through the criminal justice system.

Role of Child Welfare Systems

The Child Abuse Protection and Treatment Act mandates that states have in place "policies and procedures to address the needs of infants born with and identified as being affected by illegal substance abuse or withdrawal symptoms from prenatal drug exposure."[69] Reporting requirements for in utero illicit substance exposure to child welfare systems have been interpreted differently by each state. More than 25% of states currently have statutes that consider illicit substance use during pregnancy to be reportable as child abuse or neglect.[32] Health care providers caring for pregnant women with substance use disorders and their infants should be knowledgeable about their state requirements and be able to educate women during pregnancy. Notably, although the incidence of NAS has increased in recent years,[2,7] federal funding for child welfare systems has not changed,[70] even as some state child welfare systems are reporting an increased workload attributable to NAS.[71] In recent years, Congress has addressed the issue of substance-exposed infants in child welfare systems; however, there has not been a substantial increase in funding to state child welfare systems to bolster the response to the growing number of opioid-exposed infants. There is an urgent need for improved funding to child welfare systems to ensure the safety of infants and to promote the well-being of families.

RECOMMENDATIONS

Opioid use in pregnancy is increasingly common, with an associated increase in opioid-exposed infants. This critical public health issue demands a public health approach grounded in science. For these reasons, the AAP recommends the following:

1. The treatment of pregnant women with substance use disorder requires a coordinated, evidence-based, public health approach. The AAP reaffirms its position that punitive measures taken toward pregnant women are not in the best interest of the health of the mother-infant dyad.
2. Primary prevention strategies should be bolstered to educate the public about the addictive potential of prescription opioids and enhance access to reproductive health services, including effective forms of contraception such as LARC.
3. The ACOG policy that universal substance use screening of all pregnant women via validated screening tools such as questionnaires should occur at routine health care visits and at several points throughout prenatal care and be applied equally to all women, regardless of age, race, ethnicity, or socioeconomic status, should be supported. If urine drug testing is performed, a reasonable effort to obtain a woman's informed consent should be made before collecting the sample, and the woman should be aware of the results and who will have access to the results.
4. Access should be improved to comprehensive prenatal care for pregnant women with substance use disorders, including medication-assisted treatment and gender-specific substance use treatment programs that provide nonjudgmental, trauma-informed services.
5. Health care providers caring for women who use substances during pregnancy should be knowledgeable about their state's reporting mandates around illicit drug use and educate pregnant women prenatally about these requirements. In addition, states should clarify which substances constitute mandated reporting and explicitly define the health care provider's role in reporting.
6. To adequately ensure the safety of substance-exposed infants and to provide optimal care to families, social support services and child welfare systems are in need of additional funding.

The American College of Obstetricians and Gynecologists supports the value of this clinical document as an educational tool (December 2016).

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ABBREVIATIONS

AAFP: American Academy of Family Physicians
ACOG: American College of Obstetricians and Gynecologists
LARC: long-acting reversible contraception
NAS: neonatal abstinence syndrome

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A Public Health Response to Opioid Use in Pregnancy

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ORIGINAL ARTICLE

Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012

SW Patrick[1,2,3,4], MM Davis[5,6,7], CU Lehman[1,2,8] and WO Cooper[1,3,4]

OBJECTIVE: Neonatal abstinence syndrome (NAS), a postnatal opioid withdrawal syndrome, increased threefold from 2000 to 2009. Since 2009, opioid pain reliever prescriptions and complications increased markedly throughout the United States. Understanding recent changes in NAS and its geographic variability would inform state and local governments in targeting public health responses.

STUDY DESIGN: We utilized diagnostic and demographic data for hospital discharges from 2009 to 2012 from the Kids' Inpatient Database and the Nationwide Inpatient Sample. NAS-associated diagnoses were identified utilizing *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. All analyses were conducted with nationally weighted data. Expenditure data were adjusted to 2012 US dollars. Between-year differences were determined utilizing least squares regression.

RESULTS: From 2009 to 2012, NAS incidence increased nationally from 3.4 (95% confidence interval (CI): 3.2 to 3.6) to 5.8 (95% CI 5.5 to 6.1) per 1000 hospital births, reaching a total of 21 732 infants with the diagnosis. Aggregate hospital charges for NAS increased from $732 million to $1.5 billion ($P < 0.001$), with 81% attributed to state Medicaid programs in 2012. NAS incidence varied by geographic census division, with the highest incidence rate (per 1000 hospital births) of 16.2 (95% CI 12.4 to 18.9) in the East South Central Division (Kentucky, Tennessee, Mississippi and Alabama) and the lowest in West South Central Division Oklahoma, Texas, Arkansas and Louisiana 2.6 (95% CI 2.3 to 2.9).

CONCLUSION: NAS incidence and hospital charges grew substantially during our study period. This costly public health problem merits a public health approach to alleviate harm to women and children. States, particularly, in areas of the country most affected by the syndrome must continue to pursue primary prevention strategies to limit the effects of opioid pain reliever misuse.

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INTRODUCTION

Neonatal abstinence syndrome (NAS) is a withdrawal syndrome that occurs in opioid-exposed infants shortly after birth.[1–3] Infants with NAS have longer, more complicated postnatal hospitalizations characterized by a myriad of clinical signs ranging from feeding difficulty to seizures.[1,4,5] Recently, NAS emerged as a significant public health problem, increasing in number and healthcare expenditures.[5] By 2009, one infant was born per hour with the syndrome, accounting for an estimated $720 million in hospital charges.[5] The increase in NAS occurred temporally with an increase in opioid pain reliever (OPR) use[6] among several populations, including pregnant women.[7,8]

Data from the Centers for Disease Control and Prevention suggest that since 2009, when the most recent national estimates of NAS were reported, OPR use continued to increase. In 2012, the total number of OPR prescriptions rose to 259 million, enough for every American adult to have one bottle.[9,10] Recent data also highlight substantial variation in OPR use across different United States geographic regions.[9] To date, however, there are no national studies describing geographic variation in NAS. Understanding recent changes in NAS, including its variability in geographic regions, would inform state and local governments in targeting public health responses.

We sought to determine whether the incidence of NAS increased since 2009 in parallel with the marked increase in OPR use nationally and whether the incidence varied across the United States. Further, we aimed to determine whether healthcare utilization patterns of infants with NAS changed over time.

METHODS

Study design and setting

For this retrospective serial cross-sectional analysis, we used data from the Kids' Inpatient Database (KID) for 2009 and 2012 and from the Nationwide Inpatient Sample (NIS) for 2010 and 2011. Both data sets are compiled by the Agency for Healthcare Research and Quality as part of the Healthcare Utilization Project. The KID is the largest publicly available all-payer database for hospitalized children in the United States. The KID contains 2 to 3 million pediatric inpatient records per year from 2500 to 4100 hospitals and is created through systematic random sampling to select 10% of uncomplicated term births and 80% of other pediatric discharges. This sampling strategy gives the KID statistical power to evaluate rare conditions and provide more precise point estimates for all pediatric conditions.[11] The NIS is the largest publicly available all-payer inpatient database in the United States, containing more than 8 million hospital stays sampled from a 20% stratified sample of 1000 community hospitals.[12] Both the KID and NIS have been used broadly in national

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studies of pediatric[5,13,14] and adult[5,15,16] conditions. As the study used de-identified data, it was considered exempt from human subjects review by the Vanderbilt University School of Medicine.

Identification of sample

Infants with NAS were identified if the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) code 779.5 (drug withdrawal syndrome in a newborn) appeared in any 1 of 25 diagnostic fields.[17] Infants with presumed iatrogenic NAS from medical treatment were excluded using strategies described previously.[5] KID and NIS provide data for hospital births using *ICD-9-CM* codes (V3000 to V3901 with the last two digits of '00' or '01') if the patient is not transferred from another acute care hospital or healthcare facility. Uncomplicated births are identified using the diagnosis-related group code for 'Normal Newborn' (391, version 24).[11,12]

Descriptive variables

Infants with NAS are more likely to have neonatal respiratory complications, feeding difficulty, seizures and low birthweight.[1] Clinical characteristics of infants were obtained using the following *ICD-9-CM* codes in any one of the diagnostic fields during the birth hospitalization: transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11, 770.12), respiratory distress syndrome (769.x), other neonatal respiratory diagnoses (770.x excluding above codes and 770.7), feeding difficulty (779.3x), concern for sepsis (771.81), jaundice (774.x) and seizure (779.0, 780.3). Additional descriptive variables, including primary payer (private, Medicaid, uninsured and other) and sex were provided in the KID and NIS.

Outcome variables

National incidence rates of NAS were estimated by dividing the total number of infants with NAS by the total number of hospital births and expressed as incidence per 1000 births. Beginning in 2012, the KID and NIS samples increased, providing sufficient reliability to create estimates by the United States Census Bureau geographic division. Length of stay (LOS) data were obtained from the KID and NIS; as infants not receiving pharmacotherapy for NAS are unlikely to have LOS >6 days,[1] we evaluated LOS for all infants with NAS and then for infants with NAS who had a LOS >6 days (presumed pharmacologically treated). Throughout the article we will refer to infants presumed to be pharmacologically treated as 'pharmacologically treated'. Hospital charges were obtained from the KID and NIS and adjusted to 2012 US$.[18] Missing charges ($<3\%$) were imputed using a regression approach using the command 'impute' with diagnosis-related groups, LOS, age and NAS as predictors. Mean charges before and after imputation were compared and were not significantly different; data with imputed values are presented.

Data analysis

Statistical analyses were conducted using Stata version 13.1 (StataCorp, College Station, TX, USA). For all analyses, survey weights provided by Healthcare Utilization Project were applied to facilitate nationally representative estimates. For 2012, differences in clinical characteristics and primary payer for infants with NAS versus all other hospital births were assessed. Trends for LOS and hospital charges were evaluated using variance-weighted least squared regression.[5] NAS incidence rates were

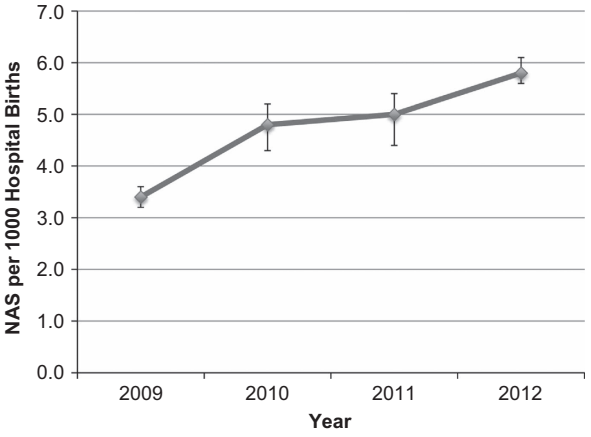
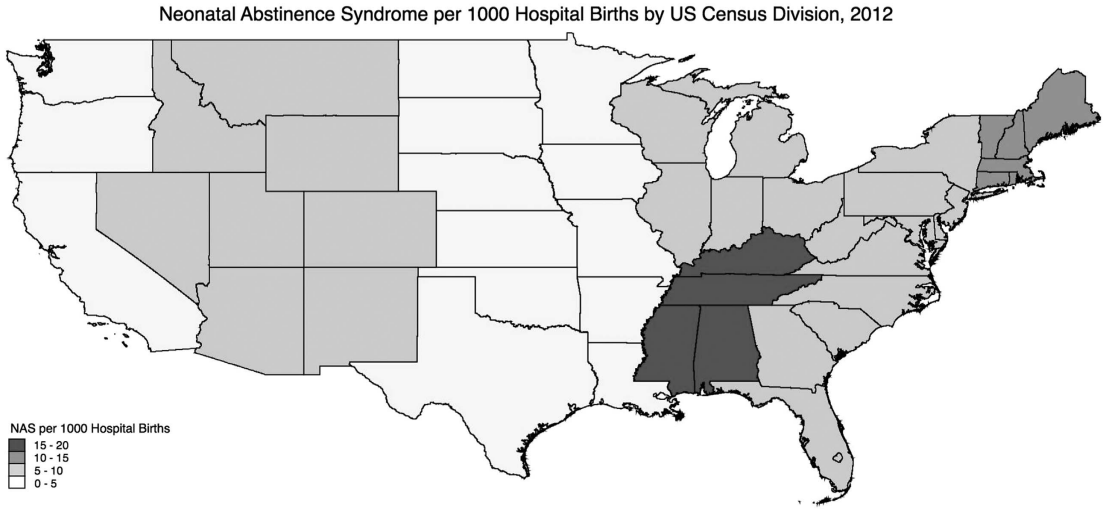


Figure 1. Incidence of neonatal abstinence syndrome per 1000 hospital births in the United States, 2009 to 2012. Data obtained from the Kids' Inpatient Database for 2009 and 2012 and from the Nationwide Inpatient Sample in 2010 and 2011. 2009: 3.4 (95% confidence interval (CI) 3.2 to 3.6); 2010: 4.8 (95% CI 4.3 to 5.2); 2011: 5.0 (95% CI 4.4 to 5.4); 2012: 5.8 (95% CI 5.5 to 6.1).

Table 1. Characteristics of infants with neonatal abstinence syndrome vs all other hospital births, 2012

	Infants with neonatal abstinence syndrome (N = *21 732*)		*All other hospital births* (N = *3 716 916*)		P-*value*
	N	%	N	%	
Female	9902	45.6	1 817 513	48.9	<0.001
Clinical characteristics					
Low birthweight	5308	24.4	267 885	7.2	<0.001
Respiratory diagnoses					
Transient tachypnea	2552	11.7	113 483	3.1	<0.001
Meconium Aspiration syndrome	613	2.8	13 235	0.4	<0.001
Respiratory distress syndrome	977	4.5	74 001	2.0	<0.001
Jaundice	7134	32.8	708 872	19.1	<0.001
Feeding difficulty	3765	17.3	111 288	3.0	<0.001
Seizures	309	1.4	4208	0.1	<0.001
Sepsis	3218	14.8	81 845	2.2	<0.001
Insurance					<0.001
Private	2688	12.4	1 717 308	46.2	
Medicaid	17 717	81.5	1 726 432	46.4	
Uninsured	853	3.9	144 137	3.9	
Other	405	1.9	118 918	3.2	

Point estimate (standard error) *N* for NAS = 21 732 (857); unweighted sample $n = 16\,254$. Point estimate (standard error) *N* for all other hospital births = 3 716 916 (55 864); unweighted sample $n = 1\,094\,748$.



US Census Division	NAS Rate per 1000 Births (95% CI)
New England	13.7 (12.5-14.5)
Middle Atlantic	6.8 (5.9-7.6)
East North Central	6.9 (6.0-7.8)
West North Central	3.4 (3.0-3.8)
South Atlantic	6.9 (6.3-7.4)
East South Central	16.2 (12.4-18.9)
West South Central	2.6 (2.3-2.9)
Mountain	5.1 (4.6-5.5)
Pacific	3.0 (2.7-3.3)

Figure 2. Incidence of neonatal abstinence syndrome per 1000 hospital births by US Census Bureau geographic division, 2012. Division 1 (New England): Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Connecticut. Division 2 (mid-Atlantic): New York, Pennsylvania and New Jersey. Division 3 (East North Central): Wisconsin, Michigan, Illinois, Indiana and Ohio. Division 4 (West North Central): Missouri, North Dakota, South Dakota, Nebraska, Kansas, Minnesota and Iowa. Division 5 (South Atlantic): Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia and Florida. Division 6 (East South Central): Kentucky, Tennessee, Mississippi and Alabama. Division 7 (West South Central): Oklahoma, Texas, Arkansas and Louisiana. Division 8 (Mountain): Idaho, Montana, Wyoming, Nevada, Utah, Colorado, Arizona and New Mexico. Division 9 (Pacific): Alaska, Washington, Oregon, California and Hawaii.

calculated by division (nine overall: New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific) for 2012. Maps were generated to evaluate geographic variation of NAS using the spmap command[19] in Stata, with map data obtained from the National Oceanic and Atmospheric Administration.[20] Throughout our analysis, all tests were two sided, with data reported with standard errors or 95% confidence intervals (CIs).

RESULTS

In 2012, there were an estimated 21 732 (95% CI: 20 052 to 23 413) infants diagnosed with NAS and 3 716 916 (95% CI: 3 607 375 to 3 826 456) other hospital births. Infants with NAS were more likely to have complications than other hospital births, including low birthweight (24.4% vs 7.2%), transient tachypnea of the newborn (11.7% vs 3.1%), meconium aspiration syndrome (2.8% vs 0.4%), respiratory distress syndrome (4.5% vs 2.0%), jaundice (32.8% vs 19.1%), feeding difficulty (17.3% vs 3.0%), seizures (1.4% vs 0.1%) and possible sepsis (14.8% vs 2.2%; $P < 0.001$). Infants with NAS were also more likely than other hospital births to be insured by Medicaid (81.5% vs 46.4%; $P < 0.001$; Table 1).

From 2009 to 2012, incidence (95% CI) of NAS increased from 3.4 (3.2 to 3.6) to 5.8 (5.5 to 6.1) per 1000 hospital births overall (Figure 1). By 2012, approximately one infant was born every 25 minutes in the United States with the syndrome. There was significant geographic variation in NAS diagnoses. In the most recent studyyear, the East South Central division (Kentucky, Tennessee, Mississippi and Alabama) had the highest incidence of NAS at 16.2 (12.4 to 18.9) per 1000 hospital births compared with the West South Central division (Oklahoma, Texas, Arkansas and Louisiana) that had the lowest national incidence rate of 2.6 (2.3 to 2.9) per 1000 hospital births (Figure 2).

From 2009 to 2012, there was no significant change in overall mean LOS for all NAS infants, pharmacologically treated NAS infants and for uncomplicated term infants with mean LOS in 2012 of 16.9 (16.0 to 17.7), 23.0 (22.2 to 23.8) and 2.1 (2.1 to 2.1) days, respectively. Inflation-adjusted mean hospital charges increased for all groups and in 2012 reached $66 700 (61 800 to

Table 2. Mean length of stay and inflation-adjusted hospital charges for all infants with neonatal abstinence syndrome, infants with neonatal abstinence syndrome with a length of hospital stay >6 days and uncomplicated term infants, 2009–2012

Year	*2009* N *(95% CI)*	*2010* N *(95% CI)*	*2011* N *(95% CI)*	*2012* N *(95% CI)*
Neonatal abstinence syndrome				
Mean length of stay (days)	16.5 (15.9–17.2)	17.2 (15.8–18.5)	16.6 (15.1–18.1)	16.9 (16.0–17.7)
Mean hospital charges (2012 US$)	53 800 (49 400–58 300)	59 000 (49 600–68 400)	62 300 (52 900–71 700)	66 700 (61 800–71 600)
Pharmacologically treated neonatal abstinence syndrome				
Mean length of stay (days)	22.7 (21.9–23.4)	22.9 (21.6–24.1)	22.8 (21.5–24.2)	23.0 (22.2–23.8)
Mean hospital charges (2012 US$)	75 700 (69 500–82 000)	80 500 (68 000–93 100)	87 700 (76 300–99 100)	93 400 (86 900–100 000)
Uncomplicated term infant				
Mean length of stay (days)	2.1 (2.1–2.1)	2.1 (2.1–2.1)	2.1 (2.1–2.1)	2.1 (2.1–2.1)
Mean hospital charges (2012 US$)	2800 (2700–2900)	3500 (3300–3800)	3700 (3400–3900)	3500 (3400–3600)

Abbreviation: CI, confidence interval. All US$ inflation adjusted to 2012 and rounded to nearest hundred.

Table 3. Aggregate hospital charges by primary payer for neonatal abstinence syndrome, 2009–2012

Year	*2009*		*2010*		*2011*		*2012*		
	Total charges ($)	*SE ($)*	*Total charges ($)*	*SE ($)*	*Total charges ($)*	*SE ($)*	*Total charges($)*	*SE ($)*	p-for-trend
Private	133 553 300	11 176 700	167 466 500	24 810 000	208 363 300	30 929 400	202 233 600	12 054 400	<0.001
Medicaid	563 809 300	33 650 300	865 649 700	79 181 000	903 654 700	94 344 100	1 170 206 600	68 789 500	<0.001
Uninsured	20 079 300	1 603 200	35 995 700	4 906 100	30 842 700	4 735 100	40 370 800	3 004 500	<0.001
Other	14 248 300	2 628 000	29 379 400	6 807 800	30 117 700	8 011 000	33 395 300	4 890 800	<0.001
Total	731 841 300	40 290 000	1 098 996 200	98 050 800	1 174 848 900	117 316 500	1 449 389 600	76 698 100	<0.001

All US$ inflation adjusted to 2012 and rounded to nearest hundred.

71 600) for infants with NAS, $93 400 (86 900 to 100 000) for pharmacologically treated NAS infants and $3500 (3400 to 3600) for uncomplicated term infants (Table 2).

During the study period, the aggregate hospital charges for NAS nearly doubled from an estimated total of $731 841 300 in 2009 to $1 449 389 600 in 2012. Through all study years the majority of hospital charges were attributed to state Medicaid programs, growing from $563 809 300 to $1 170 206 600 (Table 3, $P < 0.001$).

DISCUSSION

The incidence of NAS in the United States nearly doubled during our study period and has grown nearly fivefold since 2000.[5] NAS results in longer, more costly and complicated hospital stays compared with other hospital births. The rapid rise in NAS parallels the increase in OPR use in the United States, suggesting that preventing opioid overuse and misuse, especially before pregnancy, may prevent NAS. NAS is a rapidly increasing public health problem that merits a focused public health approach to mitigate its now far-reaching impact.

We found significant geographic variation in NAS that parallels variations in OPR prescription.[9] We found high rates of NAS in New England (Maine, New Hampshire, Vermont, Massachusetts, Rhode Island and Connecticut; 13.7, 95% CI: 12.5 to 14.5) and the East South Central (Kentucky, Tennessee, Mississippi and Alabama; 16.2, 95% CI: 12.4 to 18.9) divisions. The New England division contains two of the top five prescribing states of long-acting OPR (Maine and New Hampshire) and the East South Central division contains three of the top five prescribing states of short-acting OPR (Alabama, Tennessee and Kentucky),[9] further supporting the association between increased OPR prescription and NAS.

As expected, we found that infants with NAS were more likely to have low birthweight, significant respiratory complications including meconium aspiration and respiratory distress syndrome, feeding difficulties, possible sepsis and seizures—all of which may have contributed to longer LOS compared with other hospital births. More difficult to measure are the associated costs to families affected by the syndrome. Hospitalization for NAS most commonly involves an admission to a neonatal intensive care unit that disrupts maternal and infant bonding. Preventing NAS will prevent the clinical complications of the syndrome and potentially improve the outcomes that are more difficult to measure, including maternal attachment.[21]

Infants with NAS had an overall mean LOS of 16 days and those requiring pharmacologic treatment had a mean LOS of 23 days. We hypothesize that overall mean LOS is positively skewed by some infants who are non-pharmacologically treated or show minimal signs of withdrawal. Interestingly, LOS did not change significantly for either group during the study period. Care for NAS is variable,[4,22] and research suggests that LOS may have decreased with protocol adherence,[23] use of clonidine as an adjunct,[24] breastfeeding when appropriate (for example, when the mother is enrolled in treatment),[25–27] rooming in[28,29] and a site of care outside of the neonatal intensive care unit environment.[30]

Notably, some cases of NAS in our cohort likely occurred in the setting of medication-assisted treatment (MAT) with methadone or buprenorphine. For pregnant women with opioid dependency, current evidence suggests that enrollment in MAT improves pregnancy outcomes including preterm birth.[31,32] However, the literature supporting MAT in pregnancy was developed in the context of heroin use; data supporting optimal management of pregnant women with OPR dependency are limited.[31] With increasing use of OPR in pregnancy,[7] there is an urgent need for research to guide appropriate management of OPR dependency in pregnancy.

Nationally, over 80% of infants with NAS are enrolled in state Medicaid programs, accounting for the majority of the estimated

$1.5 billion in total hospital charges for the syndrome. Given the length of NAS-related hospital care, some states incur substantial expenditures in their Medicaid programs for NAS. For example, the Tennessee Medicaid program estimates that infants with NAS accounted for 1.7% of live births but 13.0% of expenditures on births in 2012.[33] In addition to administering and partially funding Medicaid, states also regulate prescribers and pharmacists. Therefore, states are well positioned to employ public health interventions aimed at preventing OPR misuse. Prescription drug monitoring programs are an intervention employed in every state except Missouri.[34] Prescription drug monitoring programs vary in scope and structure and are a tool to prevent behaviors that increase risk of OPR-related complications (for example, targeting doctor shopping to mitigate risk of overdose death[35]).

Limitations

Our study contains limitations that merit discussion. First, our reliance on administrative data may lead to misclassification bias. There are few studies comparing administrative to clinical data; however, one study noted that administrative data systematically underreported actual NAS.[36] Next, it is possible that the increase in NAS we observed is secondary to observer bias, as the syndrome has received significant attention recently. However, the temporal increases in NAS we observed mirror national increases in OPR use and adverse effects (for example, overdose deaths) attributed to their use. Further, our finding of significant geographic variability in the diagnosis of NAS correlated with geographic variations in use and adverse effects in the United States.[9] In addition, it is important to note that hospital charges do not equal hospital costs and do not include professional fees. In our analysis, we assumed that infants with NAS who had a LOS < 7 days were not pharmacologically treated; however, this may not always be true.

CONCLUSION

NAS has grown nearly fivefold since 2000, accounting for an estimated $1.5 billion in annual hospital expenditures across the United States. This costly public health problem merits a public health approach to alleviate harm to women and children. Federal and state policymakers should be mindful of the impact the OPR epidemic continues to have on pregnant women and their infants, and consider these vulnerable populations in efforts aimed at primary prevention. Finally, efforts aimed at primary prevention and treatment improvements should be targeted at the most affected areas of the country.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The sponsor had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript or the decision to submit.

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Prescription Opioid Epidemic and Infant Outcomes

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abstract

BACKGROUND AND OBJECTIVES: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is poorly described. Our objectives were to identify neonatal complications associated with antenatal opioid pain reliever exposure and to establish predictors of neonatal abstinence syndrome (NAS).

METHODS: We used prescription and administrative data linked to vital statistics for mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. A random sample of NAS cases was validated by medical record review. The association of antenatal exposures with NAS was evaluated by using multivariable logistic regression, controlling for maternal and infant characteristics.

RESULTS: Of 112 029 pregnant women, 31 354 (28%) filled ≥1 opioid prescription. Women prescribed opioid pain relievers were more likely than those not prescribed opioids ($P < .001$) to have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%) and to smoke tobacco (41.8% vs 25.8%). Infants with NAS and opioid-exposed infants were more likely than unexposed infants to be born at a low birth weight (21.2% vs 11.8% vs 9.9%; $P < .001$). In a multivariable model, higher cumulative opioid exposure for short-acting preparations ($P < .001$), opioid type ($P < .001$), number of daily cigarettes smoked ($P < .001$), and selective serotonin reuptake inhibitor use (odds ratio: 2.08 [95% confidence interval: 1.67–2.60]) were associated with greater risk of developing NAS.

CONCLUSIONS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of NAS.

WHAT'S KNOWN ON THIS SUBJECT: Although opioid pain relievers are commonly prescribed in pregnancy, their association with neonatal outcomes is not well described. Further, factors associated with development of neonatal abstinence syndrome, a neonatal opioid withdrawal syndrome is inadequately understood.

WHAT THIS STUDY ADDS: Prescription opioid use in pregnancy is common and strongly associated with neonatal complications. Antenatal cumulative prescription opioid exposure, opioid type, tobacco use, and selective serotonin reuptake inhibitor use increase the risk of neonatal abstinence syndrome.

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Dr Patrick conceptualized the study, conducted the analysis, and drafted the initial manuscript; Dr Cooper was involved in the analytic plan, conducted the analysis, interpreted the results, and revised the manuscript; Ms Dudley and Dr Harrell conducted the analysis, were involved in interpretation of the results, and revised the manuscript; Drs Martin, Warren, Hartmann, Ely, and Grijalva were involved in the analytic plan and interpretation of the results and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Recently, sales of opioid pain relievers (OPRs) in the United States have surged.[1] Complications of this increase have affected a wide range of the US population, including pregnant women and their infants.[2,3] Neonatal abstinence syndrome (NAS) is a postnatal withdrawal syndrome, initially described among heroin-exposed infants,[4] that presents with a wide array of clinical signs ranging from feeding difficulties to seizures.[5] From 2000 to 2009, the number of infants in the United States diagnosed with NAS grew nearly threefold, temporally associated with a fourfold increase in OPR prescriptions.[1,6] By 2009, one US infant was born per hour with NAS, accounting for $720 million in national health care expenditures.[6] Despite this temporal association, no large population-based studies have explored the association between OPR use in pregnancy and NAS.

Factors that determine which exposed infants will develop NAS are poorly understood. Rates of NAS among infants exposed to heroin or maintenance medications are reportedly as high as 80%.[5,7] For infants exposed to maintenance medications, risk of NAS seems unrelated to opioid dose[8,9]; however, the association of cumulative opioid exposure for nonmaintenance OPRs and NAS has not been studied. Some reports suggest that the use of tobacco and coprescription of selective serotonin reuptake inhibitors (SSRIs) may also increase the likelihood of developing NAS.[10–12]

Using a large retrospective cohort of pregnant women, our objectives were to identify neonatal complications associated with antenatal OPR exposures and to determine if antenatal cumulative prescription opioid exposure, opioid type, number of cigarettes smoked daily, and SSRI use were associated with a higher likelihood of developing NAS.

METHODS

Study Design and Setting

This retrospective, longitudinal cohort study was conducted by using data from TennCare, Tennessee's Medicaid program; outpatient prescription claims were linked to vital records and hospital and outpatient administrative data. These resources have been used extensively to assess the safety of medications during pregnancy.[13–16] Medicaid serves as an ideal program to study NAS because an estimated 80% of infants with NAS nationwide are enrolled in state Medicaid programs.[6]

The present study was approved with a waiver of informed consent by the Vanderbilt University institutional review board, the State of Tennessee Department of Health, and the Bureau of TennCare.

Cohort Assembly

Maternal and infant dyads were included in the study if: (1) the mother was 15 to 44 years old at the time of delivery; (2) the mother had been enrolled in TennCare at least 30 days before delivery; and (3) the infants were enrolled in TennCare within 30 days after delivery. Last menstrual period and date of delivery were obtained from vital records.[17] Pregnancies were included if the birth occurred between January 1, 2009, and December 31, 2011. Of a total 134 450 births, 112 029 met our inclusion criteria (83.3%).

Exposures

The study's primary exposure of interest was any prescription opioid fill during pregnancy identified from TennCare pharmacy claims data. TennCare pharmacy files contain information on all outpatient prescriptions that are reimbursed by TennCare. Opioid drug types were categorized as short-acting (eg, oxycodone hydrochloride), long-acting (eg, oxymorphone hydrochloride extended release), or maintenance (eg, buprenorphine hydrochloride) medications. Opioid doses were converted to morphine milligram equivalents by using established conversion guidelines to facilitate meaningful comparisons.[18] Duration of opioid use was defined as the period between the prescription start date and the end of the days of supply (allowing up to a 5-day carryover period from previous prescriptions). SSRI prescriptions filled within 30 days before delivery were captured. Information on tobacco use during pregnancy was obtained from birth certificates and from claims by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM),[19] diagnostic codes (tobacco: 305.1, V15.82, 989.84, and 649.0x). Data regarding the number of cigarettes smoked per day were obtained from birth certificates, and medication costs were obtained from TennCare pharmacy expenditures. Antenatal exposure to benzodiazepines[20] has been associated with more severe NAS among opioid-exposed infants and was considered in our evaluation; however, the use of these drugs was rare in the study population (167 of 112 029) due to TennCare policies and was not included.

Descriptive Variables, Demographic Characteristics, and Outcomes

Maternal Characteristics

Demographic information was obtained, including maternal age, education (number of years), birth number (parity), and race from birth certificates. Given that the literature describes opioid-using populations to be at increased risk of hepatitis B,[21] hepatitis C,[21,22] HIV,[23] depression,[24–26] and anxiety,[27] data regarding these conditions were obtained from birth certificate data and from outpatient and hospital administrative records by using diagnostic codes (hepatitis B: 070.2x and 070.3x; hepatitis C: 070.41, 070.44, 070.51, 070.54, and 070.7x; HIV: 042, 079.53, and V08;

depression: 296.2x, 296.3x, and 311; and anxiety disorder: 300.x). Acute pain, chronic pain, headache or migraine, and musculoskeletal diseases were identified by using ICD-9-CM codes (acute pain: 338.1x; chronic pain: 338.2x; headache or migraine: 339.x, 346.x, and 784.0; diseases of the musculoskeletal system and connective tissue: 710.x–739.x) as potential OPR indications. Lastly, we identified women with opioid dependency (opioid-type dependence: 304.0x; combinations of opioid type drug with any other drug dependence: 304.7x).

Outcome

Infants with NAS were identified if the ICD-9-CM code 779.5 (drug withdrawal syndrome in newborn) appeared in any diagnostic field during the birth hospitalization. To establish the accuracy of administrative coding for NAS, a chart review was performed of 228 randomly selected cases and noncases. Using a standard definition of NAS as a reference, ICD-9-CM–based identification yielded an 88.1% (95% confidence interval [CI]: 83.3–91.7) sensitivity and a 97.0% (95% CI: 93.8–98.5) specificity (Supplemental Information Appendix A). Infants were further classified as having: (1) no opioid exposure; (2) opioid exposure without NAS; or (3) NAS.

Infant Characteristics

After establishing our cohort, our goal was to describe the clinical characteristics of each infant based a priori on the literature. NAS is characterized by respiratory symptoms, feeding difficulties, and seizures. Opioid-exposed infants and infants with NAS are also more likely to be born preterm or with a low birth weight.[5] Gender, gestational age, and birth weight data were obtained from birth certificates. Clinical signs of NAS, including transient tachypnea of the newborn (770.6), meconium aspiration syndrome (770.11 and 770.12), respiratory distress syndrome (769.x), other neonatal respiratory diagnoses (770.x, excluding the aforementioned codes and 770.7), feeding difficulty (779.3x), and seizure (779.0 and 780.3), were obtained from hospital claims. Infants with NAS might be at greater risk for concerns of sepsis (771.81) considering their clinical presentation (eg, irritability, respiratory distress), and they may also be at an increased risk of jaundice (774.x) due to feeding difficulties. We evaluated for necrotizing enterocolitis (777.5x), given that some authors have reported an association between this condition and NAS.[28] Lastly, we examined the risk of hemolytic disease (773.x) among infants with NAS because of the possibility of previous maternal intravenous drug use.

Data Analysis

The Wilcoxon rank-sum test and χ^2 tests were used where appropriate for bivariate analyses. Candidate predictors of NAS were established a priori from the literature. The level of missing data in our predictors was evaluated; <1% of missing data was found for all variables except number of cigarettes smoked per day, which had 5.6% missing. Birth weights <400 g were deemed unreliable and considered missing. To account for missing data, we used the aregImpute function for multiple imputation by using predictive mean matching[29,30] with 5 imputations. Because of the small numbers of long-acting opioids (n = 177), this group was combined with maintenance opioids for the statistical analyses. Using our entire cohort of 112 029 pregnant women, a logistic regression model was fit with NAS as the outcome and cumulative opioid exposure, opioid type (short-acting, long-acting, or maintenance), number of cigarettes smoked per day, SSRI within 30 days of delivery, infant gender, birth weight, multiple gestations, year of birth, birth number (parity), maternal age, maternal education, and maternal race (white, African American, and other) as predictors. The nonlinear relationship of continuous variables was accounted for by using restricted cubic splines for all variables except morphine milligram equivalents, which were cube root transformed and fit by using a quadratic function to account for skewness.[29] Results for nonlinear predictors are presented graphically (with P values for tests of association) because odds ratios would compare arbitrary data points and may not fully capture their nonlinear relationship with the primary outcome (ie, NAS). Interactions were tested between opioid type × cumulative opioid exposure, number of cigarettes smoked per day × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and SSRI × cumulative opioid exposure.

Because OPR use early in pregnancy would likely not result in NAS, 2 supplemental analyses restricted to opioid prescriptions were performed that continued through the final 30 and 14 days of pregnancy to determine if restriction to these subsets changed our results. Cost estimates were created by using TennCare pharmacy expenditures and previously published estimates of NAS hospitalization charges.[6] All dollars were adjusted to 2011 US dollars by using the Consumer Price Index.[31] Statistical analyses were completed by using R version 3.1.0. (R Foundation for Statistical Computing, Vienna, Austria)[32] and Stata version 13.0 (StataCorp, College Station, TX).

RESULTS

Among the 112 029 pregnant women in our sample, 31 354 (28.0%) were prescribed at least 1 OPR during pregnancy. Compared with women with no opioid exposure, women taking OPRs were more likely ($P <$ .001) to be white (72.4% vs 65.8%); have depression (5.3% vs 2.7%), anxiety disorder (4.3% vs 1.6%),

headache or migraine (8.3% vs 2.0%), and musculoskeletal disease (23.7% vs 5.8%); use tobacco (41.8% vs 25.8%); and be prescribed an SSRI within 30 days before birth (4.3% vs 1.9%) (Table 1).

Among women prescribed opioids, the majority received short-acting medications (n = 30 192 [96.2%]); fewer received maintenance treatment of opioid use disorder (n = 853 [2.7%]) or long-acting preparations (n = 177 [0.6%]) (Supplemental Table 4). Median (interquartile range) cumulative morphine milligram equivalents were higher among those using maintenance medications (18 480 [8160–37 232]) compared with those using long-acting preparations (4029 [1508–10 800]) or short-acting preparations (150 [75–373]; $P <$ .001). Median (interquartile range) amounts paid for OPRs per individual were $1317 (586–2598) for maintenance treatment, $208 (53–756) for long-acting preparations, and $8 (5–16) for short-acting preparations. Within the last 30 days of pregnancy, 8835 women were prescribed OPRs, 93.6% of whom received a short-acting preparation (Supplemental Table 5). Lastly, 12 896 women received a >7 days' supply of opioids during pregnancy (Supplemental Table 6).

In our cohort, a total of 1086 infants were diagnosed with NAS, 701 (65%) of whom had mothers with at least 1 OPR prescription during pregnancy. Between 2009 and 2011, the quarterly rate of NAS among infants in TennCare rose from 6.0 to 10.7 per 1000 births ($P <$ .001) (Fig 1). NAS occurred more frequently among infants exposed to maintenance opioids (29.3%) and long-acting opioids (14.7%) than in those exposed to short-acting preparations (1.4%) (Supplemental Table 4). Infants with NAS were more likely than other opioid-exposed and nonopioid-exposed infants to be born with a low birth weight (21.2% vs 11.8% vs 9.9%; $P <$ .001) and preterm (16.7% vs 11.6% vs 11.0%; $P <$ .001). Consistent with the characteristics of the syndrome, when comparisons were made between nonopioid and opioid-exposed infants, those with NAS were more likely ($P <$ .001) to have respiratory diagnoses (28.7% vs 10.1% vs 8.8%), feeding difficulties (13.1% vs 2.6% vs 2.3%), and seizures (3.7% vs 0.4% vs 0.3%). Rates of necrotizing enterocolitis were similar among all groups (Table 2). Every $1 spent on short-acting and long-acting opioids (excluding maintenance) was associated with $52 and $12, respectively, in hospital charges for infants with NAS.

After adjusting for maternal age, education, race, infant gender, birth weight, multiple births, birth number (parity), year of birth, the interaction of opioid type × cumulative opioid exposure, opioid type × number of cigarettes smoked per day, and number of cigarettes smoked per day × cumulative opioid exposure, the following factors were independently associated with an increased odds of NAS: cumulative opioid exposure for short-acting OPRs ($P <$ .001), opioid type ($P <$ .001), number of cigarettes smoked per day ($P <$ .001), and SSRI use within 30 days of delivery (odds ratio: 2.08 [95% CI: 1.67–2.60]) (Fig 2). For pregnant women exposed to maintenance/long-acting opioids, the risk of NAS was consistently higher than in other exposure groups, but the risk did not vary with cumulative opioid exposure (P = .16). In supplemental analyses, restricting assessments to women who filled OPR prescriptions through 30 and 14 days before delivery, our results were similar to the findings from our primary analysis (Supplemental Tables 7 and 8, respectively).

TABLE 1 Maternal Characteristics According to Opioid Exposure in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (n = 80 675)		Any Opioid (n = 31 354)		P
	Median	IQR	Median	IQR	
Age, y	23	20–27	24	21–27	<.001
Education, y	12	12-13	12	11–13	<.001
Birth number	1	1–2	1	1–2	<.001
	N	%	*N*	%	
Race					<.001
Black	25 986	32.2	8362	26.7	
White	53 074	65.8	22 699	72.4	
Other	1298	1.6	188	0.6	
Maternal comorbidities					
Pain					
Musculoskeletal disease	4430	5.8	7439	23.7	<.001
Headache or migraine	1636	2.0	2593	8.3	<.001
Chronic pain	40	0.0	187	0.6	<.001
Acute pain	72	0.1	132	0.4	<.001
Infectious					
Hepatitis C	328	0.4	358	1.1	<.001
Hepatitis B	91	0.1	39	0.1	.61
HIV	144	0.2	43	0.1	0.13
Psychiatric					
Depression	2185	2.7	1672	5.3	<.001
Anxiety disorder	1279	1.6	1361	4.3	<.001
Opioid dependency	154	0.2	262	0.8	<.001
Additional substances used					
Tobacco	20 785	25.8	13 097	41.8	<.001
SSRI (last 30 d of pregnancy)	1529	1.9	1335	4.3	<.001

Percentages may not add to 100% because of rounding.
IQR, interquartile range.

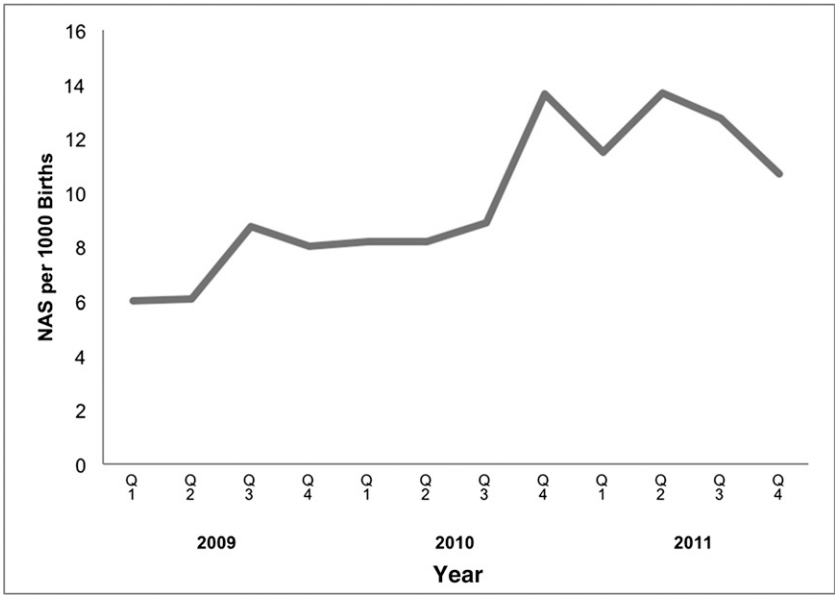

FIGURE 1
Rate of NAS in Tennessee Medicaid according to quarter, 2009 through 2011. $P < .001$.

Based on our regression model, the predicted probability of NAS among mothers who received OPRs during pregnancy varied greatly depending on drug type, cumulative opioid exposure, and number of cigarettes smoked per day. As an example, a woman who took oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks, who smoked 20 cigarettes (ie, 1 pack) per day and took an SSRI, had a 0.366 (95% CI: 0.270–0.474) probability of her infant having NAS (Table 3).

TABLE 2 Infant Characteristics for Infants With and Without NAS in Tennessee Medicaid, 2009–2011

Characteristic	No Opioid (No NAS) (n = 80 292)		Opioid (No NAS) (n = 30 651)		NAS (n = 1086)		P
	N	%	*N*	%	*N*	%	
Female	39 064	48.7	14 986	48.9	502	46.2	.2
Preterm (<37 wk)	8868	11.0	3549	11.6	181	16.7	<.001
Low birth weight (<2500 g)	7940	9.9	3615	11.8	230	21.2	<.001
Clinical conditions							
Respiratory diagnoses	7052	8.8	3083	10.1	312	28.7	<.001
Transient tachypnea of the newborn	2192	2.7	964	3.1	146	13.4	<.001
Respiratory distress syndrome	2170	2.7	1045	3.4	76	7.0	<.001
Meconium aspiration syndrome	321	0.4	106	0.3	36	3.3	<.001
Other respiratory diagnoses	4517	5.6	1965	6.4	177	16.3	<.001
Jaundice	13 963	17.4	5503	18.0	393	36.2	<.001
Feeding difficulty	1809	2.3	788	2.6	142	13.1	<.001
Sepsis	1515	1.9	692	2.3	78	7.2	<.001
Seizure	240	0.3	117	0.4	40	3.7	<.001
Hemolytic disease	1051	1.3	342	1.1	28	2.6	<.001
Necrotizing enterocolitis	136	0.2	56	0.2	**	0.1	.7

Comparisons made among mutually exclusive groups of no opioid exposure and no NAS, opioid exposure and no NAS, and NAS. Percentages may not add to 100% because of rounding.
**Value suppressed given n <10 in cell.

DISCUSSION

In this large retrospective cohort study of >100 000 pregnancies, cumulative OPR exposure for short-acting OPRs, opioid type, tobacco, and SSRI use during pregnancy was associated with an increased risk of NAS. In the study cohort, nearly 1 in 3 women used at least 1 OPR during pregnancy; 96% were nonmaintenance prescription opioids. Although NAS has previously been associated with illicit opioid use, we found that 65% of infants with NAS were exposed to legally obtained OPRs in pregnancy. These associations provide compelling evidence that OPRs and other concurrent antenatal exposures have a measurable deleterious impact on infants who are more likely than others to be born with NAS and related complications.

Maintenance medications were categorized separately, given that women using maintenance medications have different risks and different reasons for using opioids. For women with heroin dependency especially, maintenance medications have been shown to improve both maternal and neonatal outcomes, including improved fetal growth and decreased preterm birth.[33,34]

Neonatal Complications

Rates of NAS nearly doubled in TennCare during our 3-year study period, reaching 10.7 per 1000 births, exceeding previously reported rates of 3.4 per 1000 births.[6] Compared with nonopioid-exposed infants, those with NAS were more likely to have neonatal complications. Opioid-exposed infants and those with NAS were more likely than nonopioid-exposed infants to be born preterm and have low birth weight. Preterm birth imparts risk to the infant for clinical comorbidities, including respiratory distress syndrome, feeding difficulties, and jaundice (as we have shown).

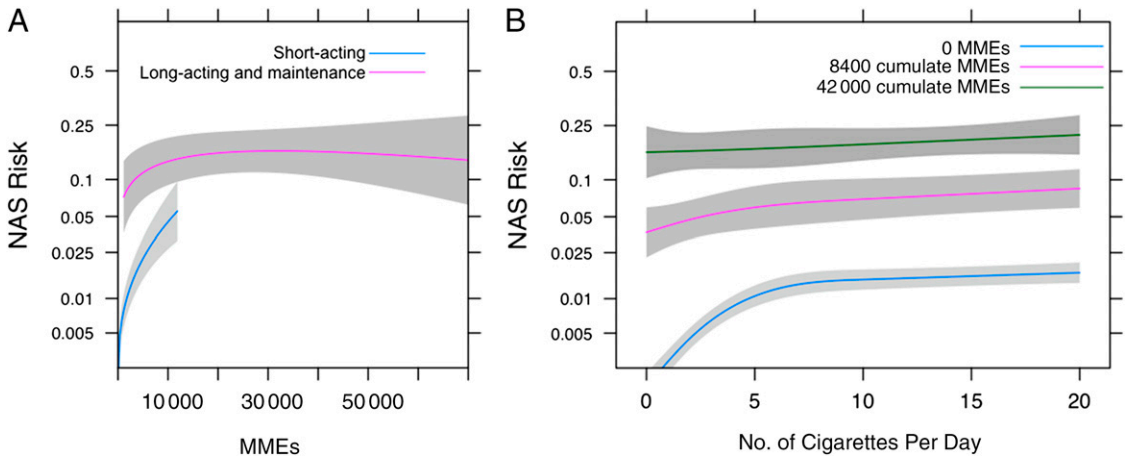

FIGURE 2

Probability of NAS. A, Opioid type and cumulative morphine milligram equivalents (MMEs). B, Number of cigarettes smoked per day and cumulative MMEs after adjusting for maternal characteristics, infant characteristics, and birth characteristics. Graph A: Cumulative MMEs and risk of NAS for short-acting opioid preparations ($P < .001$) and long-acting/maintenance opioid preparations ($P = .16$). Graph B: An increasing number of cigarettes raised the risk of NAS among women with 0 cumulative MME (ie, receiving no legal opioids; $P < .001$) receiving a cumulative total of 8400 MMEs, which equals oxycodone 10 mg q6h × 20 weeks ($P < .001$), and 42 000 MMEs, which equals buprenorphine 24 mg daily × 25 weeks ($P < .001$). The absolute risk and 95% CIs of NAS have been adjusted for cumulative opioid dose in MMEs, maternal age, maternal education, birth number, infant birth weight, year of birth, maternal race, infant gender, multiple gestations, and interaction effects of drug type × cumulative opioid dose ($P = .002$), number of cigarettes smoked per day × cumulative opioid dose ($P < .001$), and drug type × number of cigarettes smoked per day. Total sample = 112 029 mother–infant dyads, 30 651 mothers with OPR use, and 1086 infants with NAS.

In this study cohort, opioid dose for short-acting opioids, tobacco use, and SSRI use were strongly associated with NAS. Similar to previous smaller studies, we found that dose of maintenance opioids did not modify the risk of NAS.[8,9] Furthermore, our findings provide important information that builds on previous studies of OPR use in pregnancy[3,35,36] and several publications describing tobacco and SSRI use in the context of opioid maintenance.[10–12] Both tobacco and SSRIs have been described in the literature as having individual withdrawal syndromes and unique toxidromes.[5] Nevertheless, these exposures could also be associated with a constellation of other risk factors that may be difficult to measure directly (eg, substance abuse) and account for in our analyses. Polysubstance exposure is common among infants with NAS, raising the possibility that observable clinical signs (eg, hypertonia) may not be solely attributable to opioids. In many instances, clinical signs compatible with NAS may be due to multiple withdrawal syndromes and toxidromes occurring simultaneously.

State Policies

The association of increasing use of OPR, overdose deaths, and NAS garnered the attention of many state and federal policymakers.[37] States license and regulate prescribers and pharmacists, and they are financially responsible for the care received by ~80% of infants with NAS through Medicaid programs.[6,38] Nearly all states have implemented prescription drug monitoring programs[39] that aim to reduce diversion and misuse of OPR by identifying high users and high-risk behavior (eg, "doctor and pharmacy shopping"). Tennessee's program began in 2006 as an optional resource for providers and pharmacists. In 2013, the state instituted a requirement that the program must be queried before prescribing most controlled substances.[40] Our study found that ~30% of pregnant women in TennCare were prescribed at least 1 opioid before these policy changes. It will be important moving forward to evaluate the impact of new state policies on reducing opioid use in pregnancy and the incidence of NAS. Furthermore, innovative strategies to enhance prescription drug monitoring databases by including risk predictions of adverse outcomes such as NAS and overdose deaths[41] should be piloted and evaluated.

Variable Risk

The American Academy of Pediatrics recommends that all opioid-exposed infants be observed in the hospital for 4 to 7 days after birth.[5] However, our data suggest there was a wide variability in an infant's risk of drug withdrawal based on opioid type, dose, SSRI use, and number of cigarettes smoked per day by the mother (Fig 2, Table 3). Future studies should evaluate new care models for opioid-exposed infants at different risk levels of developing NAS. For instance, some low-risk infants may be safely discharged from the hospital sooner, whereas high-risk infants may require longer hospital observation.

Limitations

Our study does have several important limitations to consider, similar to other studies that rely on accurate coding of

TABLE 3 Probability of NAS According to Varying Exposures of Short-Acting Opioids and Maintenance Opioids, Tobacco, and SSRI Use

Variable	Short-Acting (eg, Oxycodone Hydrochloride) 10 mg q6h	Maintenance (eg, Buprenorphine Hydrochloride Tablet) 24 mg q24h
	Probability (95% CI)	Probability (95% CI)
5-wk duration	0.011 (0.008–0.016)	0.132 (0.085–0.199)
No cigarette use, SSRI use	0.023 (0.016–0.034)	0.241 (0.157–0.351)
5 cigarettes/d, no SSRI	0.026 (0.020–0.033)	0.165 (0.123–0.219)
5 cigarettes/d, SSRI	0.053 (0.039–0.071)	0.293 (0.217–0.383)
20 cigarettes/d, no SSRI	0.037 (0.029–0.047)	0.179 (0.137–0.231)
20 cigarettes/d and SSRI use	0.074 (0.056–0.098)	0.314 (0.239–0.399)
25-wk duration	0.048 (0.028–0.081)	0.163 (0.103–0.247)
No cigarette use, SSRI use	0.095 (0.055–0.158)	0.289 (0.188–0.416)
5 cigarettes/d, no SSRI	0.073 (0.045–0.115)	0.172 (0.123–0.236)
5 cigarettes/d, SSRI	0.141 (0.088–0.220)	0.303 (0.218–0.404)
20 cigarettes/d, no SSRI	0.104 (0.068–0.156)	0.216 (0.156–0.291)
20 cigarettes/d and SSRI use	0.196 (0.129–0.285)	0.366 (0.270–0.474)

Results shown after adjustment for maternal age, education, race, infant gender, birth weight, year of birth, interaction drug type and cumulative opioid exposure (0.0002), interaction of number of cigarettes smoked per day and cumulative opioid exposure ($P < .001$), and interaction of drug type and number of cigarettes smoked per day.

Probability can be interpreted as 1 = 100% certainty that an event will occur, and 0 = 0% certainty that an event will occur. As an example, a probability of an outcome equal to 0.37 can be interpreted as among a sample of 100 patients, 37 will have the predicted outcome.

As an example, a woman taking oxycodone hydrochloride 10 mg every 6 hours for 5 weeks with no tobacco or SSRI use had a probability of delivering an infant with NAS of 0.011 (95% CI: 0.008–0.016). In contrast, a woman prescribed buprenorphine hydrochloride 24 mg daily for 25 weeks smoking 20 cigarettes (ie, 1 pack) per day and taking SSRIs had a 0.366 (95% CI: 0.270–0.474) probability of delivering an infant with NAS.

hospital administrative and vital statistics data. Both errors of omission and commission are possible, leading to misclassification bias; however, our medical record review suggested that potential misclassification of outcomes was likely to be small. Next, we did not directly observe women in our cohort taking the prescribed OPR. It is possible that OPR medications were not taken as prescribed, resulting in a bias toward the null hypothesis. Next, we were unable to capture other exposures (eg, illicit drugs) that may have influenced our primary outcome (NAS). Opioids obtained by other legal sources not paid for by TennCare (ie, cash payments) were not captured in our sample, which could bias our results toward the null hypothesis. Conversion to morphine milligram equivalents, although the accepted standard, may not create perfect comparisons of various OPRs. Finally, it is possible that opioid prescribing is a surrogate for other unmeasured risk factors for NAS; residual confounding cannot be completely ruled out.

CONCLUSIONS

The use of commonly prescribed, nonmaintenance OPRs in pregnancy increased the infant's risk of developing NAS. Nearly 27% of our cohort of pregnant women was prescribed at least 1 short-acting OPR. Furthermore, NAS risk varied widely based on antenatal cumulative opioid exposure, opioid type, number of cigarettes smoked per day, and SSRI use. Public health efforts should focus on limiting inappropriate OPR and tobacco use in pregnancy. Prescribing opioids in pregnancy should be done with caution because it can lead to significant complications for the neonate.

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THE HIGH COST OF WORKING: *My daughter has begun the search for a summer job or internship. Last year, she was quite fortunate as she found a paid internship in a city only 5 hours from where we live. The company, a provider of wellness packages, seemed a great fit given my daughter's interest in athletics and communication. That she was actually paid to rotate through the different departments and assist in a variety of functions made the experience all the more remarkable. One of my sons, looking for a position overseas, has not been so fortunate.*

As he has found out, and as reported in The New York Times *(Education Life: February 5, 2015), few paid overseas internships exist. Students either volunteer or pay someone else for the opportunity to do an internship. The demand for overseas positions is high. During the 2012-13 year, approximately 40,000 Americans participated in for-credit internships or interned, worked, or volunteered abroad for no credit. Given the demand for positions, companies have sprung up to arrange for internships in a wide array of industries across the globe. While the experiences can be quite gratifying and many students report that the experience helped them find a job back home in the US, the costs of obtaining the internship can be high. Students may have to pay between $8,000 and $15,000 for a six to eight week experience. The cost of the flight and food are additional. While I am supportive of overseas learning experiences, I am having a bit of trouble digesting the concept of paying so much money for the opportunity. I am hoping that my children find summer internships close to home.*

Noted by WVR, MD

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