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**SMOKING IN PREGNANCY**

In this issue of *WMJ*, authors explore a variety of topics related to maternal and child health, including trends and risk factors of secondhand smoke exposure in pregnant women, plus a program that aims to help them quit smoking.

Cover design by Kendi Neff-Parvin
CASE REPORTS

Febrile Infection-Related Epilepsy Syndrome Treated Successfully With Anakinra in a 21-Year-Old Woman ........................................................................................................... 135
Cecilia Westbrook, MD, PhD; Thanuja Subramaniam, MD; Ryan M. Seagren, PharmD; Erick Tarula, MD; Dominic Co, MD; Meghan Furstenberg-Knauff, APNP; Adam Wallace, MD; David Hsu, MD, PhD; Eric Payne, MD

Triple Diagnosis of Crohn's Disease, Celiac Disease, and Eosinophilic Esophagitis in a Child With Siderius-Hamel Syndrome .................................................................. 140
Rajni Ahlawat, MD; Nirzar S. Parikh, MD; Ajay Jhaveri, MBBS, DNB

YOUR PROFESSION

Dean's Corner
The Value to Academic Medicine of the Association of American Medical Colleges ................................................................. 145
Joseph E. Kerschner, MD

Immunosuppression-Free Kidney Transplantation: Advancing New Treatments by Building on Our Past Foundations.......................................................... 146
Dixon B. Kaufman, MD, PhD; Peiman Hematti, MD; Robert N. Golden, MD
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A message from Wisconsin Department of Justice, Brad Schimel, Attorney General, and the Wisconsin Department of Health Services
Advocating for Our Youngest Victims: Wisconsin's Approach to Testing Drug-Endangered Children

Hillary W. Petska, MD, MPH; Ann E. Budzak-Garza, MD; Arne H. Graff, MD; Judy Guinn, MD; Kristin C. Iniguez, DO; Barbara L. Knox, MD; Carolyn R. Nash, MD; Rita Ventura, DNP; Lynn K. Sheets, MD

S

ubstance abuse in the United States is a public health crisis. The opioid epidemic claims more than 130 lives every day.1 Marijuana is becoming increasingly available as more and more states legalize it. Methamphetamine use in Wisconsin increased 462% between 2010 and 2017.2 And in 2018, Wisconsin was ranked as the worst state in the country for excessive drinking.3

But what is less obvious from the headlines is the impact this crisis is having on children. One in 8 children in the United States lives in a household with a parent with alcohol and other drug abuse (AODA) issues.4 In 2016, approximately half of all human drug exposures reported to US Poison Centers involved children less than 6 years of age.5 Medical providers in Wisconsin are seeing drug-endangered children regularly, whether or not they know it.

In addition to the direct risk of harm, having a parent with a substance use disorder is an adverse childhood experience that can lead to short- and long-term health consequences, such as diabetes, hypertension, heart disease, liver disease, cancer, and stroke.6 These children are also at increased risk of child maltreatment and have higher rates of mental and behavioral disorders.6 Substance abuse is also often associated with additional adverse childhood experiences (eg, caregiver with a mental health disorder, domestic violence) that lead to accumulation of risks.7 Children in these homes can even have drugs in their systems but are not easily identified. Screening for drug endangerment needs to include children who are identified as at-risk, but no national consensus currently exists on when and how pediatric drug testing should be performed.

In early 2019, Wisconsin medical providers specializing in child maltreatment convened to develop a consensus statement regarding this issue. Consensus was reached in regard to overarching principles, indications for testing, preferred biologic substrates, scope of drugs included in the test, and limits to testing. Overall, the purpose of pediatric drug testing should be to promote the health, safety, and well-being of children. Detection of a drug-exposed child provides a window of opportunity in which medical providers can advocate for our youngest victims.

Detection of a drug-exposed child provides a window of opportunity in which medical providers can advocate to improve a child’s life course trajectory. This often leads to referrals to child protective services and law enforcement in order to facilitate safety and services for children and families. Detection of an illicit drug or nonprescribed pharmaceutical should lead to a safety assessment but does not by itself indicate parental drug use or the need for out-of-home care.

Medical providers frequently perform drug testing when there is concern for drug exposure, such as in children with altered mental status, suspected ingestion, or suicide attempt. Testing is also often sought for children found in drug-endangered environments and should be considered in children with concerns for child physical abuse.8 Drug testing of adolescents requested by caregivers should not be pursued without the youth’s knowledge and consent.9 Many institutions address drug testing in their general policies on consent, although institutional policies vary.

Available drug tests vary significantly in detection thresholds, automatic/reflexive confirmation of positive results, range of drugs detected, and substrates tested (eg, urine, hair, blood). Ideally, pediatric drug tests should utilize an easily available substrate, be highly sensitive, include a broad range of drugs, and have reflexive confirmation of any positive results.9

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Any lab utilized should be CLIA certified. In Wisconsin, the substrate used varies based on current best evidence, local environment (eg, proximity of medical care), nuances of multidisciplinary relationships, and clinical judgment. Urine testing is well-standardized and studied and is the most common sample used for drug testing in primary care. It can detect systemic exposure typically within the last 3 days. Hair testing can detect but not differentiate environmental and/or systemic exposure that occurred within the past 3 months. Due to its long window of detection, hair testing is not clinically useful for the child with signs of acute intoxication. Attempts to time the exposure by using hair segmentation should be avoided. Results of hair testing also can be affected by hair structure, growth rate, melanin content, hygiene, and cosmetic treatments and must be interpreted carefully to prevent misuse in child protection cases. Qualitative and quantitative blood testing should be considered if a child is symptomatic and time of exposure is known as it may help estimate the amount of drug a child was exposed to.

Rapid urine drug screens commonly used in emergency departments (ED) should be used only to guide medical treatment in an altered child but are not forensically defensible. Many EDs use urine drug screens developed for adults, most of which detect drugs of abuse at workplace thresholds. Thus, false negatives can occur when the drug of abuse is present but below a workplace limit of detection. However, in young children, any level of exposure may signal a threat to their health and safety. In addition, many drugs may be missed with these screens, including nonprescribed pharmaceuticals and synthetics (eg, fentanyl). Without confirmation, there is also a possibility of a false positive, which can have serious implications for children and families.

In such cases, a more comprehensive urine screen also should be performed. Any positive result must be interpreted in the context of the evaluation, investigation, and limitations of the test. Although a comprehensive review is beyond the scope of this commentary, there are several specific examples that should be noted due to their relative frequency in clinical practice and potential for harm:

- If possible, urine testing should be performed immediately after removal from a drug-endangered environment, as a positive result after placement in a new environment may represent exposure in either setting.
- A positive result on hair testing in children up to 12 months of age may represent in utero drug exposure.
- A positive result for methamphetamine should lead to consideration of which isomer is present, as the l-isomer can be found in over-the-counter nasal preparations and other prescription medications unlike the d-isomer, which can only result from exposure to 3 substances (ie, prescription methamphetamine [Desoxyn], benzphetamine [Didrex], or street drugs).
- A negative result does not rule out exposure as a child may be exposed to a substance not on the testing panel or the substance may be present at a level too low to be detected or outside the window of detection.
- Safety decisions should not rely on retesting unless there is a new concern, as a positive result may indicate the initial or ongoing exposure and a negative result may indicate no ongoing exposure or missed detection.

Once identified, any child with concern for drug-endangerment should be tested for drugs followed by an urgent medical evaluation, ideally within 48 hours. Given their increased risk of physical, developmental, academic, and emotional consequences, enhanced periodicity and mental health are also important considerations in drug-endangered children.

The opioid epidemic, legalization of marijuana, the presence of widely prescribed psychoactive substances and other factors will guarantee that drug endangerment of children will continue long into the future. As health care providers, we have a duty to develop best practices regarding drug testing of children that are based on scientific evidence.

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Financial disclosures: None declared.

REFERENCES

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Smoking in Pregnancy

Sarina Schrager, MD, MS, WMJ Associate Editor

The 1964 Surgeon General’s report on the health effects of smoking described “incontrovertible evidence” that smoking was linked to detrimental health outcomes in almost every organ system.1 Prior to this report, there was controversy about whether smoking caused any medical illnesses. To follow up, a 2001 Surgeon General’s report on women and smoking described the vast, negative impact of smoking on a developing fetus.2

Yet, despite this evidence, in 2016, over 11% of pregnant women in Wisconsin smoked, significantly higher than the national average of 7%.3 Two papers in this issue of WMJ focus on smoking in pregnant women in Wisconsin. The paper by Garg, et al, describes a downward trend in exposure to secondhand smoke of nonsmoking pregnant women.4 Secondhand smoke does not confer the same level of risk as smoking itself, but can cause negative effects to the mother and fetus. At baseline, pregnant women in Wisconsin are at 40% higher risk of secondhand smoke exposure than the US average. Pregnant women who are teens or African American are at highest risk of exposure. However, there has been a downward trend over the last 5 years. This paper outlines future research priorities focused on ways to further decrease smoking and exposure to secondhand smoke in the pregnant population.

The second paper by Alaniz, et al, describes updates and expansion to the First Breath program.5 Developed by the Wisconsin Women’s Health Foundation in 2000, the First Breath program trains staff at health care facilities throughout Wisconsin to provide evidence-based education about smoking cessation in pregnancy. The program was successful in reaching pregnant women but noticed a high relapse rate. They also noticed that as the years progressed, they were not reaching as many women due to declines in staffing at several of their sites. The paper in this issue of WMJ describes updates to the First Breath Program that expand access and continue education into the postpartum period. The newly expanded program will continue to work with women up to 6 months postpartum.

Focusing on smoking cessation of women, even after the baby is born, may affect long-term smoking habits of children going into adolescence.6 Strong evidence documents that children of smokers or former smokers are at much higher risk of smoking themselves. Telling parents about this risk may be a strong motivation for them to quit themselves.

Even 55 years after the original Surgeon General’s report on smoking and health, the medical community and other patient advocacy groups work to improve health by counseling patients to decrease or quit smoking. Especially in the high-risk community of pregnant women and their children, medical professionals should continue to be vigilant about advocating for smoking cessation.

REFERENCES

Travel During Pregnancy: A Study of Postpartum Women in Madison, Wisconsin

Lauren Melidosian, BS; Elizabeth Evans, BS; Katharina Stewart, MD; Kathleen M. Antony, MD, MSCI

ABSTRACT

Problem Considered: While travel during pregnancy is increasingly common, both the act of traveling and the destination itself may pose risks to pregnant women. Thus, it is relevant to ask pregnant women about travel for individual care and to assess how often pregnant women travel. Based upon our prior study, we hypothesized that domestic travel would be common, with approximately 30% of pregnant women traveling, and that international travel also would be common, with approximately 5% of the population traveling. We also hypothesized that maternal characteristics, such as socioeconomic status, country of birth, and parity, would affect domestic and international travel during pregnancy.

Methods: In order to study trends in travel by pregnant women, a survey was conducted among postpartum women at Meriter Hospital in Madison, Wisconsin, between October 17, 2016 and March 21, 2017.

Results: Of the 61 postpartum women surveyed, 75.4% had traveled domestically and 11.4% had traveled internationally while pregnant. Those who traveled domestically had a significantly higher level of education ($P = 0.025$) and higher annual income ($P = 0.001$) compared to women who did not travel domestically. There were no differences in these characteristics between those who did and did not travel internationally. Women traveling domestically were less likely to discuss their travel plans with their obstetrician when compared to women traveling internationally (67.4% v 85.7%, respectively). Out of 19 canceled trips, both domestic and international, 4 women opted to cancel their trips due to concerns about Zika virus (21.1%).

Conclusions: This study allowed for an in-depth look at pregnant travelers and their reasons for traveling and for canceling their trips. When travel plans were discussed, in most instances (94.6%), the obstetrician initiated the conversation. As pregnant women travel both domestically and internationally at increasing rates, it is important to discuss risks associated with travel.

INTRODUCTION

As travel during pregnancy becomes more and more common, it is imperative to address concerns regarding both the mother and the fetus, as being away from a maternity care provider for any amount of time can be dangerous, especially if complications arise during travel.1-8 The safest time for pregnant women to travel is during the second trimester, because women in their first and third trimesters tend to experience more complications.4,5 Historically, concerns for air travel included noise, turbulence, cosmic radiation, low oxygen saturation, venous thromboembolism, infectious diseases related to air travel, and delivery en route.5,9 Fortunately, these risks are relatively low as long as the mother has no comorbid medical conditions.4 Regardless, some pregnant women may choose car travel to allow for more flexibility, but this mode of transportation is also not risk-free.

Historical data demonstrate that most pregnant travelers remain within the United States; however, some travel internationally, potentially exposing these women to infectious diseases.5,10 Exposure to Zika virus and malaria while pregnant pose real threats for the fetus, and malaria can have serious effects on both the mother and fetus.5,11,12 Malaria can cause preterm delivery, low birth weight, congenital infection, spontaneous abortion, stillbirth, and even maternal death.5,11 Pregnant women are more likely than non-pregnant women to contract malaria.5,11 Zika virus also has been shown to cause adverse pregnancy outcomes. The most common effects are microcephaly and other brain abnormalities.5,12 Parts
of the United States have been affected by Zika virus in the past; however, there were no documented cases of local mosquito-borne transmission of Zika virus in the United States in 2018 or 2019 (to date).

In this study, we sought to estimate the prevalence of travel during pregnancy in the population of women delivering at our health system in Madison, Wisconsin, by surveying recently postpartum women about domestic and international travel during their pregnancy. Our secondary purpose was to provide insight regarding whether travel and its risks and benefits were discussed with the obstetric providers. Based upon our prior study querying women at approximately 18 to 22 weeks gestation, we hypothesized that domestic and international travel would be common, occurring in approximately 30% and 5% of the study population, respectively. We also hypothesized that maternal characteristics, such as socioeconomic status, country of birth, and parity, would affect domestic and international travel during pregnancy.

METHODS

This study was approved by the UnityPoint Health-Meriter Hospital Institutional Review Board (Meriter IRB# 2016-005). All pregnant women who presented to the UnityPoint-Health birthing center for likely delivery were asked whether they gave permission to be approached about obstetric research projects (in general) during their hospital stay. Those who agreed were approached regarding participation in this study by a research coordinator during their stay on the postpartum unit. The study coordinator discussed the specific purpose, as well as the risks and benefits of the study. Ample time was provided for the woman to decide whether she wanted to participate. After she chose to participate, verbal consent was obtained.

The questionnaire was administered in the participant’s hospital room by study personnel who asked the questions aloud and marked answers on paper. It took approximately 5 to 15 minutes to complete. No data were collected from the participants’ medical records, and no personal health information was collected on the forms. All maternal characteristics and demographic factors presented here were self-reported by the participant.

Women were approached regarding completion of this questionnaire between October 17, 2016 and March 21, 2017. For the purpose of this study, domestic travel was defined as a distance exceeding 60 miles. International travel was defined as travel to another country or travel outside of the contiguous United States, thus travel to Alaska, Hawaii, and United States territories was included within the definition of international travel.

Descriptive statistics were calculated; chi-square, Fisher exact, and Student t tests were performed where appropriate. All data were entered into Excel (Microsoft Excel, 2013, Redmond, Washington), and all statistical analyses were performed using SPSS 25.0 (IBM Corporation. Released 2017. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

RESULTS

Sixty-six women agreed to be approached about participating in obstetric research in general between October 17, 2016 and March 21, 2017. Of those approached, 61 women agreed to participate in the study and completed the questionnaire. Reasons women refused (after initial agreement) included unexpected admission.
to the neonatal intensive care unit, loss of interest in participating, and visitors in the postpartum room at the time of approach. Maternal characteristics for domestic and international travelers compared to nontravelers are shown in Tables 1 and 2. The age range of participants was 19 to 45, with the average age being 31.8 years. All participants self-identified as female.

Of the 61 participants, 46 traveled domestically (75.4%) and 7 traveled internationally (11.5%) during their pregnancy. Seven (11.5%) participants traveled both domestically and internationally; 9 (14.8%) participants did not travel domestically or internationally. In order to illustrate where participants traveled domestically, a map of the United States was created (Figure 1). Women who traveled domestically had a higher education level ($P=0.025$) and a higher annual income ($P=0.001$) compared to women who did not travel domestically. Domestic trips were due to family (78.8%), leisure/vacation (76.9%), work (36.5%), family emergency or unplanned travel (9.6%), and pregnancy or medical reasons (1.9%). International travel was for leisure/vacation (85.7%) and for work (14.3%) (Table 3). Of those who traveled domestically, 8 (13.1%) traveled to Florida and 3 (4.9%) traveled to Texas; both states had active transmission of Zika virus during this time period.$^{13}$ Of those who traveled internationally, no one in this sample traveled to areas with active transmission of Zika virus.

Of the 19 canceled trips, 14 (73.7%) were domestic trips and 5 (26.3%) were international trips. Of the 14 canceled domestic trips, the majority were related to advanced gestational age and 2 were canceled due to Zika virus concerns (14.3%). Ten domestic trips were cancelled by women who ultimately did not travel at all domestically. Had these women traveled, then 56 (91.8%) of women sampled would have traveled domestically. Of the 5 canceled international trips, 3 were canceled due to concerns about venous thromboembolism (VTE) (60.0%) and 2 were canceled due to concerns about Zika virus (40.0%). Zika virus was considered a concern for 58.1% of domestic travelers and 66.7% of international travelers. Three international trips were cancelled by women who ultimately did not travel at all internationally. Had these women traveled, then 10 (16.4%) of women sampled would have traveled internationally.

Domestic travelers discussed their travel plans with their obstetric provider less frequently than international travelers (67.4%; 85.7%) (Table 4). Obstetric providers initiated the conversation and asked about travel 93.5% of the time for domestic travelers and 100.0% of the time for international travelers. Advice offered by providers for women traveling both domestically and internationally included frequent ambulation (74.2%, 100%), hydration (77.4%, 100%), steps to avoid food- and water-borne illnesses (19.4%, 33.3%), and steps to avoid mosquito-borne illnesses (38.7%, 33.3%).

The longest number of consecutive hours traveled by ground transport during pregnancy was 16 hours for domestic travelers (mean 5.0 hours, range 1-16 hours) and 8 hours for international travelers (mean 3.3 hours, range 1-16 hours). The longest number of consecutive hours traveled by air transport during pregnancy was 8 hours for domestic travelers (mean 3.7 hours, range 2-8 hours) and 15 hours for international travelers (mean 3.0 hours, range 2-8 hours).

### Table 2. Demographic Characteristics of Gravidae Who Traveled Internationally (or Outside the Contiguous United States) Compared to Those Who Did Not Travel

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No International Travel n=54</th>
<th>International Travel n=7</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD)</td>
<td>31.6 (5.4)</td>
<td>30.7 (4.3)</td>
<td>0.68</td>
</tr>
<tr>
<td>Advanced maternal age (n,%)</td>
<td>15 (27.8)</td>
<td>2 (28.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>45 (83.3)</td>
<td>6 (85.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>African American</td>
<td>5 (9.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.9)</td>
<td>1 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>2 (3.7)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latina</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Parity (Mean, SD)</td>
<td>17 (0.9)</td>
<td>1.3 (0.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>Tobacco use (n,%)</td>
<td>3 (5.6)</td>
<td>0 (0.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Medical problems (n,%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (7.4)</td>
<td>0 (0.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypertensive disorder of pregnancy</td>
<td>9 (16.7)</td>
<td>2 (28.6)</td>
<td>0.37</td>
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<tr>
<td>Thyroid disease</td>
<td>8 (14.8)</td>
<td>0 (0.0)</td>
<td>0.35</td>
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<tr>
<td>Asthma</td>
<td>2 (3.7)</td>
<td>0 (0.0)</td>
<td>0.78</td>
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<td>Seizures</td>
<td>3 (5.6)</td>
<td>0 (0.0)</td>
<td>0.69</td>
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<tr>
<td>Other</td>
<td>1 (1.9)</td>
<td>1 (14.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Medical complications of pregnancy (n,%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prior preterm birth</td>
<td>9 (16.7)</td>
<td>0 (0.0)</td>
<td>0.31</td>
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<tr>
<td>Preterm birth in index pregnancy</td>
<td>5 (9.3)</td>
<td>0 (0.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Prior miscarriage</td>
<td>21 (38.9)</td>
<td>1 (14.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Twins</td>
<td>3 (5.6)</td>
<td>0 (0.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Residence b</td>
<td></td>
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</tr>
<tr>
<td>Urban</td>
<td>15 (27.8)</td>
<td>1 (14.3)</td>
<td>0.55</td>
</tr>
<tr>
<td>Suburban</td>
<td>23 (42.6)</td>
<td>5 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>15 (27.8)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently married or living with partner</td>
<td>49 (90.7)</td>
<td>7 (100.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Currently widowed, divorced, separated,</td>
<td>5 (9.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>or never married/not living with partner</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest educational level</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>High school/less than high school</td>
<td>2 (3.7)</td>
<td>0 (0.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Some or completed college</td>
<td>35 (64.8)</td>
<td>3 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Graduate degree</td>
<td>17 (31.5)</td>
<td>4 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Born in the United States</td>
<td>52 (96.3)</td>
<td>6 (85.7)</td>
<td>0.31</td>
</tr>
<tr>
<td>Parents born in the United States</td>
<td>52 (96.3)</td>
<td>7 (100.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Primary household language English</td>
<td>53 (98.1)</td>
<td>7 (100.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Annual Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $50,000</td>
<td>10 (18.5)</td>
<td>0 (0.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>$50,000-149,999</td>
<td>31 (57.4)</td>
<td>3 (42.9)</td>
<td></td>
</tr>
<tr>
<td>$150,000 or more</td>
<td>13 (24.1)</td>
<td>4 (57.1)</td>
<td></td>
</tr>
</tbody>
</table>

*One participant indicated “Other.”
DISCUSSION

This study demonstrates that in the sample population of women delivering at our health care institution, 11.5% traveled internationally and 75.4% traveled domestically. Of those who traveled internationally, no one in this sample traveled to areas with active transmission of Zika virus. However, 40% of cancelled international trips were due to concerns regarding active transmission of Zika virus.

Conducting this survey allowed for an in-depth look at the travel experience for pregnant women. Our finding that more women traveled domestically than internationally is consistent with the literature. Education level and annual income reflected the ability for women to travel domestically; a higher education level is typically correlated with a higher income level, and more income allows for more travel. We speculate that if our sample size had been larger, it is likely that similar differences would have been observed for international travel as well.

The purpose of travel among gravidae in our study differed slightly from the findings in the literature, which note more international travel to visit friends and relatives. This study also showed that pregnant women traveled more frequently than expected. We hypothesized that 30% of the population would travel domestically, while our survey found that 75.4% of pregnant women travel domestically. This may be based upon differing definitions of “domestic travel.” In our prior study, we defined travel outside the state of Wisconsin as “domestic” travel, whereas in this study we counted travel within the state if it exceeded 60 miles. The difference is slightly smaller for international travel; about 5% of the population in our prior study travelled internationally, and this survey revealed that 11.4% of pregnant women traveled internationally. We also found that no women in this population travelled to areas with active transmission of Zika virus, which is lower than in our prior ultrasound-unit based study. Our prior study was performed at our tertiary care clinic, thus may have disproportionately represented women who had traveled to areas with active transmission of Zika virus, particularly if they were referred due to concerns about this exposure. The survey used in the current study also covers a larger range of travel-related topics than the prior study.

In order to determine and discuss relevant risks for pregnant women, it is critical to discuss travel plans during pregnancy. We identified that domestic travelers were less likely to discuss their travel plans with their provider than international travelers; international travel poses more risks, such as disease transmission or VTE. In most cases, the provider initiated the conversation, which is important because women may not be aware of the risks and benefits of traveling while pregnant. Participants reported that their providers were generally supportive of domestic and international travel plans (77.4%, 83.3%).

A very small number of participants decided to cancel their travel plans; most canceled trips were domestic. Of the canceled trips, 21.1% were canceled due to concerns about Zika virus. While Zika virus was a concern for 58.1% of domestic travelers at the time of data collection, there have been no documented cases of mosquito-borne transmission of Zika virus in the United States in 2018 or 2019 to date. It is hopeful this trend will continue. Regarding Zika virus internationally, active transmission also has decreased. None of the participants were concerned about malaria, which is consistent with their travel destinations. The number of cancelled trips and the reasons for cancelling suggest that appropriate discussions about travel generally occurred.

Strengths of this study include the focused nature of the questionnaire, which allowed for in-depth queries regarding the travel destinations and reasons for travel, as well as for the analysis of cancelled domestic and international trips in order to assess the
impact of Zika virus disease on travel patterns near the time of its epidemiologic peak impact.17

Limitations of this study include the low overall capture rate of pregnancies occurring during this time period, which limits the generalizability of our findings. We only approached women who had signed a permission-to-contact form regarding obstetric research in general; very few women signed the form. Since the completion of this study, our unit has changed its approach to requesting permission regarding individual studies. It may be possible that if women were asked about participating in a questionnaire (versus research in general), more would have agreed to participate, but this cannot be assessed. Generalizability of our findings is also limited by this low sample size and inclusion of women delivering at a single center in a relatively wealthy, small city. Representation of racial and ethnic minorities was low, as was representation of non-native English speakers or those born outside the United States. Finally, all women were queried about travel at the end of their pregnancy, thus our findings may be subject to recall bias.

CONCLUSION
It can be deduced that among sampled participants delivering at our institution, pregnancy is not a significant limiting factor when planning travel. We have observed a very limited effect of travel on pregnancy and birth outcomes.10 For international travel, demonstrable risks include the risk of VTE, but also the possibility of disease transmission or motor vehicular collisions once at the destination.

The obstetric provider should be aware of domestic and international incidence rates of both Zika virus and malaria, as well as other diseases that can impact pregnancy, such as Listeria, Yellow Fever, and traveler’s diarrhea, and educate the gravida accordingly. Despite the decreased rate of Zika transmission globally, it remains important for gravidae to discuss all travel plans with obstetric providers prior to the scheduled trip, particularly if certain precautions (such as immunizations or prophylactic medications) must be taken.5 Obstetric providers should continue to inquire about travel plans, as we found that most conversations about travel were, indeed, initiated by the provider.

Acknowledgements: Data from this paper were presented as a poster presentation at the Wisconsin Association for Perinatal Care (WAPC) 2019 Annual Conference, Abstract #11, Oshkosh, Wisconsin, April 7-9, 2019.


Helping Low Income Pregnant Women Quit Smoking: Improving the First Breath Program

Kristine Alaniz, MPH; Bruce Christiansen, PhD; Emily Tingting Sullivan, BS; Lisette Khalil, MS, JD; Michael C. Fiore, MD, MPH, MBA

ABSTRACT

Background: Maternal smoking during pregnancy can have dire consequences for both baby and mother. In 2000, the Wisconsin Women’s Health Foundation developed the First Breath program to address this challenge, particularly among low-income women. While this prenatal smoking cessation program was successful, 2 factors necessitated changes in the program: changes in the health care reimbursement environment and a high postpartum relapse rate.

Methods: The First Breath program was revised using the concepts of implementation science and included focus groups of First Breath clients, a randomized control trial to test new postpartum services, and an implementation project to test the new method of delivering First Breath.

Results: A year after implementing the new First Breath program, results are encouraging. First Breath expanded its reach by 34% over 2017. Eighty-eight new First Breath sites (to a total of 235 sites) have been added, resulting in increased diversity. While there was significant relapse within the new program from prenatal abstinence to 1-month postpartum abstinence (from 13.6% to 7.3% abstinence, biochemically verified, intent-to-treat) there was not additional relapse through 6 months postpartum.

Conclusion: Sustaining a valuable community-based tobacco dependence intervention program serving a vulnerable population requires continuous improvement built on measured outcomes and response to changes in the health care delivery system. First Breath may serve as a model program to aid underserved pregnant women who smoke.

BACKGROUND

Maternal smoking during pregnancy can have dire consequences for both the baby and the mother, and smoking during pregnancy is more common in disadvantaged populations. This health risk is particularly prevalent in Wisconsin where rates of smoking during pregnancy remain higher than national averages. In 2016, 11.3% of pregnant women in Wisconsin reported smoking sometime during their pregnancy, 57% higher than the national rate of 7.2%.

In 2000, the Wisconsin Women’s Health Foundation (the Foundation) developed the First Breath program to address the challenge of prenatal smoking in Wisconsin, especially among disadvantaged women. The Foundation recruited programs providing health care services to low-income pregnant women—typically county health departments—to serve as First Breath sites. The Foundation trained staff from participating clinical sites to provide brief, evidence-based cessation counseling. First Breath sites also collected limited program data and provided modest nonmonetary incentives to enrolled women. The Foundation was responsible for recruiting new First Breath sites, providing the initial training to site staff, and delivering ongoing training, support, program materials, quality assurance activities, and tracking of women enrolled in the program.

The First Breath program was successful. Between 2002 and 2017, over 16,000 women were enrolled in the First Breath program. By 2017, there were 157 active First Breath sites, including at least 1 site in 62 of the 72 Wisconsin counties. Thirty-five percent of the 2017 First Breath participants who completed the postpartum survey self-reported not smoking in the third trimester. An additional 44% reported a reduction in the number of cigarettes smoked per day.

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Corresponding Author: Bruce Christiansen, PhD, Senior Scientist, Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, 1930 Monroe St, Suite 200, Madison, WI 53711; phone 608.262.4087; email bc1@ctri.wisc.edu.
While successful, 2 factors compelled changes in the initial First Breath program: one related to a change in the external environment in which First Breath takes place and one related to outcomes. First, changes in the external environment contributed to a marked decrease in the number of women reached over time, from 1,460 in 2011 to 983 in 2017 (Figure). Many of the public health agencies that were long-term First Breath sites experienced significant reductions in funding and reimbursements, reducing their ability to provide prenatal services (including First Breath services) to the women in their communities. These changes suggested the need to change how the First Breath program was delivered. Second, even among First Breath participants, there was a high rate of relapse to smoking in the postpartum period, consistent with the literature that has documented a relapse rate of 50% to 80% after delivery, with low-income women particularly likely to relapse. And, the number of women resuming smoking increases as a function of time since delivery, with the relapse rate at 6 months postpartum exceeding that at 3 months postpartum. The high relapse rate suggested the need to extend First Breath services into the postdelivery period for up to 6 months.

This article describes how the First Breath program was redesigned to address these factors and reports on outcomes from the first year (2018) following the statewide implementation of the new First Breath program.

METHODS

Implementation science methods were used to guide First Breath changes. Implementation science assesses the processes that promote the adoption and integration of evidence-based practices, interventions, and policies into routine health care and public health settings. It holds that an intervention is more likely to be effective over time if it is based on published literature and guidelines, and changes in response to ongoing evaluation. Likewise, an intervention is more likely to be sustained over time if it adapts to changes in the external context (real world setting in which interventions are delivered). Finally, program evaluation should assess perceptions of people receiving the intervention.

There were 3 distinct steps to redesigning the First Breath program: (1) a series of focus groups and participant informant interviews, (2) a randomized control trial, and (3) an implementation/feasibility evaluation of the new program.

Focus Groups and Participant Informant Interviews

Twelve focus groups of First Breath participants (N=66) took place in 6 Wisconsin cities, and an additional 67 First Breath participants were interviewed individually to gather their perceptions of postpartum relapse. Themes from this qualitative study highlighted the importance of extending counseling into the postpartum period, including findings that women smoked as a way to manage stress (including the stress of a newborn), motivation to stay quit decreased postpartum, and there is a need for cessation help and guidance for others in the family who may not be supportive of continued abstinence. Additionally, these First Breath participants requested more comprehensive services from cessation specialists. The focus groups and participant informant interviews results were largely consistent with the literature regarding postpartum relapse. Specifically, relapse is often triggered by stress, lack of sleep, depression, and/or lack of social support. Additionally, other smokers in the household, especially the baby’s father and grandmother, negatively impact women’s smoking quit attempts and increase the risk of postpartum relapse. This literature and the results of participant input highlighted the need to extend First Breath service into the postpartum period.

Randomized Control Trial

The randomized control trial compared the original First Breath program that provided only prenatal counseling with an expanded First Breath program that also provided postdelivery counseling. For this study, women who enrolled at existing First Breath sites were contacted by Foundation staff and told about the opportunity to participate in a research project. Those who gave verbal consent were randomly assigned to either the original First Breath program (n=94) or the expanded program (n=91). Those assigned to the expanded program received additional postpartum in-home services by Foundation staff that included 1 additional prenatal home visit to acquaint the woman with the Foundation counselor and to set expectations for postdelivery counseling, as well as 3 postpartum in-home smoking cessation counseling visits and 3 post-
One of the primary outcome measures was biochemically confirmed smoking cessation (i.e., breath carbon monoxide [CO] level of <6 ppm) of the women participants at about 6 months postpartum and self-report nonsmoking in the previous 7 days (point prevalence abstinence). (Six women who reported some smoking were counted as smokers in the analysis.) Among those who completed the follow-up (n = 95 of 185), the bioconfirmed abstinence rate of nonsmoking was greater for women who received postpartum care than women in the control group (36.6% vs 12.3%, respectively, \(P < .01\)). Calculated on an intent-to-treat basis, abstinence rate was 15.5% for women who received postpartum help vs 7.4% for women in the control group (\(P = .07\)). While this difference was not statistically significant, this small study provided insights into the absolute rates of quitting.

**Implementation/Feasibility Evaluation**

This project adapted the postnatal services tested in the randomized control trial into a new delivery method that addressed the inability of current First Breath sites (primarily county agencies) to continue to provide First Breath services. In this new delivery method, rather than relying upon indigenous staff at prenatal clinic sites to provide First Breath counseling, Foundation staff provided the counseling. The role of prenatal clinic site staff was limited exclusively to referring interested pregnant women to the program. This change had an added benefit of allowing the program to expand to prenatal clinic sites that in the past were unable or unwilling to provide the First Breath counseling component. Moreover, it was believed that having Foundation staff provide all the counseling would improve outcomes, because this staff is highly specialized and fully dedicated to providing smoking cessation counseling consistently. (All Foundation staff providing counseling are Certified Tobacco Treatment Specialists.) Having Foundation staff provide counseling also addressed the high employee turnover challenges of the local public health prenatal clinical setting.

This feasibility project enrolled 201 women. Participants expressed satisfaction with services provided, and the self-report quit rate (not biochemically verified) for those who completed the redesigned program was 46%.

Based on the focus groups, randomized control trial, and implementation/feasibility evaluation results, the revised First Breath program was implemented statewide in January 2018. In this new statewide program, counseling continues postpartum via home visits and telephone. Quitting counseling and support are provided to family members and significant others if requested. Eligibility for the program remains unchanged and includes pregnant women who: (1) are current smokers who want to quit, or (2) have already quit and want help to remain quit. Prior First Breath counseling sites were converted to First Breath referral sites. All counseling and data collection are now completed by Foundation staff. Quality assurance checks are conducted quarterly (Table 2). The primary

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**Table 1. Study Conditions and Treatment Components**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original First Breath (Prenatal only)</td>
<td>• First Breath cessation counseling at least 2 prenatal visits and 1 postpartum visit delivered by First Breath site staff &lt;br&gt; • Link to Wisconsin Tobacco Quit Line &lt;br&gt; • Optional enrollment in text program to receive motivational messages &lt;br&gt; • One 6-month postpartum in-home abstinence evaluation visit (Foundation staff) &lt;br&gt; • Potential to earn $40 in gift cards</td>
</tr>
<tr>
<td>Expanded First Breath (Prenatal and Postpartum in-home visits)</td>
<td>All original First Breath Components PLUS: &lt;br&gt; • 1 prenatal and 3 postpartum in-home counseling visits &lt;br&gt; • 3 postpartum counseling phone calls &lt;br&gt; • Potential to earn $140 in gift cards</td>
</tr>
</tbody>
</table>

Abbreviation: Foundation, Wisconsin Women’s Health Foundation.

**Table 2. First Breath Program Modifications**

<table>
<thead>
<tr>
<th>Original First Breath Program</th>
<th>New First Breath Program</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Role of community sites:</strong></td>
<td><strong>Role of community sites:</strong></td>
</tr>
<tr>
<td>• Recruit and enroll clients &lt;br&gt; • Provide prenatal smoking cessation counseling &lt;br&gt; • Collect survey data at baseline, third trimester, and postdelivery</td>
<td>• Refer potential clients to Foundation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Role of Foundation staff:</strong></th>
<th><strong>Role of Foundation staff:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Establish community First Breath sites &lt;br&gt; • Initial and ongoing site staff training &lt;br&gt; • Enrollment tracking &lt;br&gt; • Receive and analyze data &lt;br&gt; • Program evaluation</td>
<td>• Establish community First Breath sites &lt;br&gt; • Enroll referred clients &lt;br&gt; • Provide prenatal smoking cessation counseling &lt;br&gt; • Provide postdelivery, in-home smoking cessation counseling &lt;br&gt; • Involve significant other at request of enrolled client &lt;br&gt; • Collect survey data at baseline, third trimester, and postdelivery &lt;br&gt; • Data analysis</td>
</tr>
</tbody>
</table>

Abbreviation: Foundation, Wisconsin Women’s Health Foundation.
outcome is biological confirmed abstinence 6 months postpartum. Secondary outcomes include patient satisfaction, achieving a smoke-free home, and reducing infant exposure to tobacco smoke.

RESULTS

Reach

In 2017, prior to the changes, providers at First Breath sites told 987 women about the program. In the first year of the new First Breath program, providers at First Breath sites referred 1,324 women, an increase of 34%. Of those women referred, 488 (37%) enrolled in the First Breath counseling program. The greatest reason for not enrolling was an inability by Foundation staff to reach the referred woman (67%), which underscores the difficulty of reaching this population. Among those who were reached, the primary reason for not enrolling was a disinterest in the program (85% of those reached), followed by not being ready to quit (5%).

First Breath continued to reach its target population—low-income women (see Table 3). Of those referred to the program, 81% were on Medicaid, 59% unemployed, and 24% did not graduate from high school. Table 3 compares those enrolled in 2018 to those enrolled in 2015 and illustrates that 2018 enrollees were slightly younger, less likely to be African American, less likely to be Hispanic/Latina, not as likely to complete high school, more likely to be unemployed, slightly more likely to be moderate to heavy smokers (11–30 cigarettes/day), less likely to have the first cigarette in the morning within 5 minutes, and more likely to be smoking at time of enrollment.

Eighty-eight new First Breath sites and 401 new providers were added in 2018. These included rural reproductive health/WIC clinics, tribal clinics, new social services agencies, obstetrical clinics, pediatric clinics, and a county jail. In 2018, there were First Breath sites in all 72 Wisconsin counties compared to 62 counties in 2017.

Services Delivered

One improvement of the First Breath program redesign was the ability to better track services delivered, because treatment was provided by Foundation staff. Thirty-nine percent of possible home visits were completed. Home visits were about 45 minutes in length. There were an additional 1,443 intervention contacts (telephone contacts, text messages), an average of 3 per enrolled woman. Telephone contacts were about 15 minutes in length. In addition, 91 partners and other caregivers of enrolled women received quitting education and/or other help.

Relapse

One hundred seventy-seven women were enrolled long enough in the new program in 2018 to reach the 6-month postpartum follow-up visit, thus permitted a tracking of relapse over time. Of these 177 women, 24 were not smoking prenatal (self-reported not smoking and passed the CO test [<6 ppm]), starting at 28 weeks gestation. (An additional 9 passed the CO test but reported some

<table>
<thead>
<tr>
<th>Age &amp; Smoking Status</th>
<th>2015 &amp; (n)</th>
<th>2018 &amp; (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13–17</td>
<td>0.6% (7)</td>
<td>0.8% (10)</td>
</tr>
<tr>
<td>18–24</td>
<td>17.2% (203)</td>
<td>25.4% (320)</td>
</tr>
<tr>
<td>25–34</td>
<td>63.5% (751)</td>
<td>59.5% (749)</td>
</tr>
<tr>
<td>35–44</td>
<td>18.2% (215)</td>
<td>14.0% (177)</td>
</tr>
<tr>
<td>≥ 45</td>
<td>0.6% (7)</td>
<td>0.2% (3)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latina</td>
<td>7.0% (82)</td>
<td>3.0% (39)</td>
</tr>
<tr>
<td>Employed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>51.5% (583)</td>
<td>59.3% (255)</td>
</tr>
<tr>
<td>Enrolled in Medicaid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79.5% (962)</td>
<td>81.3% (1076)</td>
</tr>
<tr>
<td>Smoking status 30 days prior to pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.8% (9)</td>
<td>2.2% (27)</td>
</tr>
<tr>
<td>&lt;1/day</td>
<td>2.5% (29)</td>
<td>2.2% (27)</td>
</tr>
<tr>
<td>1–5/day</td>
<td>19.1% (223)</td>
<td>16.3% (201)</td>
</tr>
<tr>
<td>6–10/day</td>
<td>29.8% (347)</td>
<td>28.9% (357)</td>
</tr>
<tr>
<td>11–20/day</td>
<td>35.7% (416)</td>
<td>37.2% (460)</td>
</tr>
<tr>
<td>21–30/day</td>
<td>7.8% (38)</td>
<td>10.4% (129)</td>
</tr>
<tr>
<td>&gt;30/day</td>
<td>4.4% (51)</td>
<td>2.8% (35)</td>
</tr>
<tr>
<td>Age of smoking onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>40.2% (473)</td>
<td>21.2% (91)</td>
</tr>
<tr>
<td>15–19</td>
<td>51.0% (601)</td>
<td>64.2% (276)</td>
</tr>
<tr>
<td>20–24</td>
<td>7.1% (84)</td>
<td>12.1% (52)</td>
</tr>
<tr>
<td>≥25</td>
<td>1.7% (20)</td>
<td>2.6% (11)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaskan Native</td>
<td>3.8% (44)</td>
<td>3.9% (48)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.4% (5)</td>
<td>0.9% (11)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>25.0% (29)</td>
<td>22.2% (276)</td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander</td>
<td>0.2% (2)</td>
<td>&lt;0.1% (1)</td>
</tr>
<tr>
<td>White</td>
<td>69.0% (802)</td>
<td>68.0% (848)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>1.4% (16)</td>
<td>4.2% (53)</td>
</tr>
<tr>
<td>Other</td>
<td>0.3% (3)</td>
<td>0.7% (9)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>3.7% (43)</td>
<td>1.4% (6)</td>
</tr>
<tr>
<td>Some high school</td>
<td>16.9% (198)</td>
<td>23.0% (100)</td>
</tr>
<tr>
<td>High school or GED</td>
<td>46.8% (548)</td>
<td>41.5% (180)</td>
</tr>
<tr>
<td>Some college/2-year</td>
<td>29.1% (341)</td>
<td>31.3% (136)</td>
</tr>
<tr>
<td>College</td>
<td>3.2% (37)</td>
<td>2.8% (12)</td>
</tr>
<tr>
<td>Postcollege education</td>
<td>0.2% (3)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>Smoking status at time of enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>78.6% (881)</td>
<td>87.5% (378)</td>
</tr>
<tr>
<td>Time to first AM cigarette</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 5 min</td>
<td>40.2% (455)</td>
<td>30.2% (114)</td>
</tr>
<tr>
<td>6–30 min</td>
<td>26.1% (296)</td>
<td>25.9% (98)</td>
</tr>
<tr>
<td>31–60 min</td>
<td>16.2% (184)</td>
<td>12.7% (48)</td>
</tr>
<tr>
<td>&gt;60 min</td>
<td>17.4% (197)</td>
<td>31.2% (118)</td>
</tr>
<tr>
<td>Treatment goal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit for good</td>
<td>86.7% (951)</td>
<td>86.4% (483)</td>
</tr>
<tr>
<td>Quit for pregnancy/lactation</td>
<td>5.1% (56)</td>
<td>6.6% (37)</td>
</tr>
<tr>
<td>Reduce</td>
<td>6.8% (75)</td>
<td>7.0% (39)</td>
</tr>
<tr>
<td>Previous quit attempts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>86.3% (895)</td>
<td>86.0% (370)</td>
</tr>
<tr>
<td>5–9</td>
<td>9.7% (101)</td>
<td>9.8% (42)</td>
</tr>
<tr>
<td>≥10</td>
<td>4.0% (41)</td>
<td>4.2% (18)</td>
</tr>
</tbody>
</table>

Abbreviation: GED, general education diploma.  
(a) Unless otherwise noted, data was collected at time of referral.  
(b) P < 0.05  
(c) Reported percentages are the percent of those that answered the question.  
(d) Data collected at enrollment call.  
(e) 2015: asked age smoking started; 2018: asked for age of regular smoking.
smoking, suggesting very light smoking.) Thirteen were abstinent at 1 month postpartum (an additional 6 passed the CO test but reported some smoking.) Thirteen were abstinent 6 months postpartum (an additional 6 passed the CO test but reported some smoking) Calculated based on those women who completed treatment at each point in time (58) (completer analysis), the abstinence rate was 41.4% (24/58) prenatal, 22.4% (13/58) 1 month postpartum, and 22.4% (13/58) 6 months postpartum. Calculated on an intent-to-treat basis in which all women with missing data are assumed to be smoking, the abstinence rates were 13.6% (24/177) prenatal, 7.3% (13/177) at 1 month postpartum, and 7.3% (13/177) at 6 months postpartum.

**Secondary Outcomes**
Among those that completed the 6-month postpartum home visit, 70% reported no infant exposure to secondhand smoke, and 68% maintained a smoke-free home. Seventy percent were confident that they would be smoke-free in a year. Sixty-seven percent rated the First Breath program “excellent” and 22% rated it “good.” One hundred percent said they would recommend First Breath to others. Among the First Breath elements, the gift cards were rated as the most valued, followed by the CO testing, and then the counseling provided at the home visit.

**DISCUSSION**
Despite successfully enrolling over 16,000 pregnant women who smoked over 15 years, changes in the health care reimbursement environment and high postpartum relapse prompted the Wisconsin Women’s Health Foundation to adapt the First Breath program. As a result of these changes, reach in 2018 increased 34% over 2017. New First Breath referral sites and new providers within those sites have been added to the referral base. There are now First Breath sites in all 72 Wisconsin counties (prior = 62 of 72). The reduced requirements for being a First Breath site (referral only, no provision of smoking cessation counseling) is probably one contributor to both the increase in women being told about the First Breath program and the broader array of organizations serving pregnant women who became First Breath sites. The Foundation now collects information about the provision of services, which will greatly enhance its ability to understand and improve the program moving forward. Regarding relapse, abstinence rates fell about 50% (from 13.6% to 7.3%, intent to treat) from prenatal to 1 month postpartum, but there was no additional decline in abstinence through 6 months postpartum. Additional clinical intervention may be necessary to address this early relapse. This recommendation is consistent with a review of the literature, which found that the most effective interventions provided at least 3 intervention contacts within the first 4 postpartum months.¹⁹

The evolution of the First Breath program over time illustrates key concepts of implementation science.²⁰,²¹ Implementation is well served by strong and varied evaluation efforts. In addition to outcomes measured via program evaluation and rigorous evaluations, such as randomized controlled trials, qualitative information and anecdotal stories of success enrich the evaluation of programs.²⁶ Dedicated time for reflection to process information during implementation is also important.²¹,²⁷,²⁸ The overall health care delivery system is changing rapidly. Such changes in the external context²¹ often negatively affect otherwise sound community programs such as First Breath. Community agencies must be willing to monitor for such changes and be prepared to adjust protocols. For First Breath, reductions in the delivery of prenatal care services overall to economically disadvantaged women in Wisconsin was one such external threat. This change contributed to the decision to shift from services being delivered by prenatal site staff to services being delivered by dedicated counselors from the Foundation. Such external threats, if successfully addressed, can lead to positive changes. For example, it will now be easier for the Foundation to ensure fidelity to treatment protocols, because it collects relevant process data and counseling is provided by fewer, dedicated Foundation employees who are trained and fully dedicated to these tasks.

Programs benefit when representatives from the target populations participate in program development, implementation, and redesign. During the First Breath program redesign, interviews and focus groups assisted in updating educational materials, evaluating program processes, and refining outreach messaging. Developing a program that is “patient-centric” requires that such individuals have roles beyond just recipient of services and providers of data.²⁰⁻³¹ For example, one of the current First Breath counselors previously received services as a First Breath client.

Organizations providing community services should be prepared for unintended consequences and opportunities. The dedicated Foundation counselors make in-home observations. This has resulted in facilitating referrals for domestic violence, breastfeeding assistance, enrollment in Wisconsin Medicaid programs, and substance abuse/mental health treatment. While this has placed additional demands on staff (for example, staff now bring naloxone to their home visits), this opportunity afforded by the home visits has permitted the First Breath program to extend its assistance to this very vulnerable population far beyond smoking cessation services.

Challenges remain. For example, only 37% of women referred to the First Breath program ultimately enroll. The methods used to contact the women and the enrollment process, including the collection of contact information and burden on referred women, are being reviewed.

**CONCLUSION**
The First Breath program has evolved throughout its life span and has now been offered to over 18,000 Wisconsin pregnant women who smoked. It continues to help pregnant Wisconsin women, especially those living in poverty, thus benefiting their infants, themselves, and their families. As a result of this evolution, First Breath is well positioned to even more effectively meet its mission. This revised program, with its emphasis on services that continue
REFERENCES


Progesterone Supplementation for the Prevention of Preterm Birth: Provider Practice in Wisconsin

Kara Hoppe, DO, MS; Renee D. Kramer, MPH; Barbara Ha, MPH; Angela Rohan, PhD; Chelsea Aeschbach, MPH; Deborah B. Ehrenthal, MD, MPH

ABSTRACT

Objective: To assess provider practice patterns on type of progesterone prescribed and barriers specific to 17α-hydroxyprogesterone caproate utilization for preterm birth prevention.

Study Design: A survey mailed to providers assessed utilization and barriers to long-acting reversible contraception and progesterone for preterm birth prevention. Data analysis included chi-square tests for homogeneity followed by post hoc tests of proportions to detect significant pairwise differences.

Results: Five hundred sixty-three of 1,695 respondents who provide prenatal care were included in the analysis. More obstetric than family medicine and midwife providers (87.4% vs 31.4% and 72.6%, respectively; P < .001) prescribed any progesterone for preterm birth prevention. More obstetric providers prescribed 17α-hydroxyprogesterone caproate (17OHP-C) compared with family medicine and midwife providers (98.1% vs 77.8% and 80.5%, respectively; P < .0001). Family medicine and midwife providers prescribed oral progesterone more often than obstetric providers (40.7% and 24.4% vs 13.1%; P < .05). System-level barriers to 17OHP-C were reported more often than patient-level barriers at a rate that was highest among family medicine and midwife providers.

Conclusion: 17OHP-C has been demonstrated to be an effective method for prevention of recurrent preterm birth. It is used significantly less—and oral progesterone is used significantly more—by family medicine and midwife providers, emphasizing the need for increased education and decreased treatment barriers for its utilization for preterm birth prevention.

INTRODUCTION

Preterm birth constitutes the leading cause of neonatal morbidity and infant mortality in the United States.1 In 2016, approximately 1 in 10 infants were born preterm nationwide; giving the United States the highest rate of preterm birth among countries in the industrialized world.3

Previous spontaneous preterm birth is the greatest risk factor for subsequent preterm birth, recurring in 35% to 50% of women at similar gestational ages.4 Several studies have demonstrated progesterone supplementation to be an effective method for prevention of recurrent preterm birth, with appropriate patient selection, clinical scenario, and route of administration.5,6 Currently, 250 mg 17α-hydroxyprogesterone caproate (17OHP-C) administered intramuscularly on a weekly basis starting at 16 to 20 weeks through 36 weeks gestation or delivery (whichever is achieved first) is the only agent approved by the Food and Drug Administration (FDA) for prevention of recurrent spontaneous preterm birth,7 and the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine both endorse its use for prevention of recurrent preterm birth in singleton pregnancies.8-10

Makena is an FDA-approved hydroxyprogesterone caproate injection. Prior to FDA approval in 2011, compounded 17OHP-C was used exclusively. Both Makena and compounded 17OHP-C are thought to have equivalent efficacy in prevention of recurrent preterm birth. Both are reimbursable by the state’s Medicaid program, are endorsed by ACOG, and were available at the time of this survey.11

However, evidence suggests 17OHP-C may be underutilized,12,13 and a variety of barriers have been identified at the patient, provider, and system levels.14 Patient barriers have
included lack of perception they are at risk of recurrent preterm birth, lack of knowledge regarding this intervention, or concerns regarding the risks or side effects of 17OHP-C. Provider barriers include lack of access or availability of 17OHP-C as well as lack of knowledge regarding its efficacy and recommendations to provide it. System barriers include issues surrounding access to health care, which may include patients presenting late to care, difficulty coordinating administration of the drug, and insurance coverage. Prior literature examining progesterone use has focused on care provided by those working in obstetric (OB) or maternal fetal medicine practices. However, much prenatal care in the United States is provided by those in family medicine and midwifery, where less is known about their practice patterns in this area or the unique barriers they face when prescribing progesterone. This is of particular importance in rural and underserved areas, where the availability of OB providers may be limited.

The purpose of this study was to assess progesterone use across a broad range of specialties and practice locations providing prenatal care, in order to identify opportunities to improve 17OHP-C utilization and impact rising rates of preterm birth. To accomplish this, we surveyed providers throughout Wisconsin to assess utilization of, and barriers to, the use of progesterone for preterm birth prevention. Specifically, the objectives were: (1) to explore the prescribing/referral patterns of progesterone for preterm birth prevention among prenatal providers; (2) to compare the progesterone formulations prescribed by providers trained in family medicine and midwifery with those trained in obstetrics and gynecology; and (3) to understand the barriers providers face to implementation of current recommendations.

**METHODS**

**Subjects and Setting**

We surveyed physicians and advanced-practice providers (APP) in obstetrics, family medicine, and midwifery holding active licenses to practice in Wisconsin. Wisconsin is a state with an urban city as well as large rural areas, and obstetrical care is provided by those trained in obstetrics and gynecology (OB), midwifery, and family medicine.

The study sample was developed from a list of licensed providers obtained from the Wisconsin Department of Safety and Professional Services. This list included information about specialty, subspecialty, licensing, demographic information (age, sex, and ethnicity), and practice or home address. Providers were sampled if they held a license in the specialty or subspecialty of obstetrics, midwifery, family medicine, or pediatrics and had a mailing address in Wisconsin or within 50 miles of the Wisconsin border (n=7,750). ArcGIS 10.2 was used to geocode all mailing addresses, and straight-line buffers were used to identify addresses meeting our 50-mile criteria. The study was deemed exempt by the University of Wisconsin-Madison Institutional Review Board.

Surveys were mailed in the fall of 2015 by the University of Wisconsin (UW) Survey Center to all OB (n=1,002) and midwife (n=323) providers, 21% of family medicine providers (n=1,000), and 47% of pediatric providers (n=675). The budget allowed for a total sample of 3,000 licensed health care providers, so we included all OB and midwife providers and randomly selected a portion of family medicine and pediatric providers. Because there are more family medicine and pediatric providers in Wisconsin than OB and midwife providers, we determined sampling all OB and midwife providers with similar amounts of family medicine and pediatric providers would provide satisfactory representation of all specialties. To ensure the sampling across specialties was similar, we employed simple random sampling using SAS 9.4 (SAS Institute Inc, Cary, North Carolina). A $5 incentive was included in the first mailing to increase response rate.

Respondents who indicated that they did not provide care to women of reproductive age (13-44 years) (n=299) or did not provide prenatal care to patients (n=787) were excluded from this analysis (Figure 1). We also excluded providers who did not indicate their specialty (n=6) and pediatricians (n=6) due to the very small sample who reported providing prenatal care (n=6).

**Survey Design**

In collaboration with the UW Survey Center, public health professionals, and women’s health physicians, an 8-page, self-administered questionnaire was developed consisting of 39 questions focused on provision of long-acting reversible contraceptives (LARC) and progesterone use for preterm birth prevention. The intention was to analyze the questions regarding use of LARC vs progesterone separately. The first portion of the survey was applicable to all respondents and asked questions pertinent to general...
The general survey questions included provider demographic characteristics (ie, sex, age, and race) practice location, and provider specialty. Questions were asked regarding scope of practice around contraception and prenatal care, including provision of progesterone supplementation for preterm birth prevention. In addition, providers were asked to indicate the setting(s) in which they practice (eg, hospital, academic medical center, private practice). The 6 geographic categories from the 2013 National Center for Health Statistics (NCHS) Urban-Rural Classification Scheme for Counties were collapsed into 3 groups: large metropolitan, small metropolitan, and rural/micropolitan.

The prenatal and/or obstetrical care providers who responded “yes” to prescribing or referring pregnant patients for any type of progesterone supplementation to prevent preterm birth were asked about the specific formulations of progesterone (Makena, compounded, vaginal progesterone, or oral progesterone) prescribed to prevent preterm birth. They also were asked to indicate any patient- or system-level barriers they encountered specifically regarding the use of compounded 17OHP-C or Makena, such as late presentation to care, lack of patient interest, medication cost, preauthorization requirements, and on-site availability of medication.

Those with APP credentials were grouped with physicians in their specialty (OB and family medicine) when their practice was similar. Midwives constituted their own group because of their independent practice. For analysis of barriers to use, we grouped Makena and compounded 17OHP-C together as “any 17OHP-C.” Barriers to 17OHP-C provision were assessed on a Likert scale, with the responses “not at all,” “a little,” “somewhat,” “quite a bit,” and “a great deal.” The responses were dichotomized, with “quite a bit” and “a great deal” representing a substantial barrier.

### Data Analysis

Because providers’ likelihood of being sampled varied by their specialty, most results were stratified by specialty. The percentage of providers reporting referral or prescribing of progesterone in their practice for the prevention of preterm birth, the type of progesterone prescribed, and barriers specific to prescribing any 17OHP-C are described. Differences in group responses were assessed using chi-square tests for homogeneity followed by post hoc tests of proportion to detect significant pairwise differences. Where noted, analyses were restricted to prescribers of any progesterone due to substantial missing data on key items among nonprescribers. A P-value of <0.05 was considered statistically significant. All analyses were performed with STATA version 15.0 (College Station, Texas).

### RESULTS

The overall survey response rate was 56.5% (n=1,661), with 59.7% of OB providers, 53.2% of family medicine, and 65.5% of midwife providers responding. Of the 563 providers who reported providing prenatal or obstetrical care, 64.1% practiced in OB

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**Table 1. Personal and Practice Characteristics of Wisconsin Prenatal/Delivery Providers, by Provider Specialty (n=563)**

<table>
<thead>
<tr>
<th>Provider Specialty</th>
<th>Obstetrics N=361</th>
<th>Family Medicine N=87</th>
<th>Midwifery N=115</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>245 (67.9)</td>
<td>57 (65.5)</td>
<td>113 (98.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 35</td>
<td>56 (15.5)</td>
<td>21 (24.1)</td>
<td>18 (15.7)</td>
<td>0.006</td>
</tr>
<tr>
<td>35-44</td>
<td>49 (13.6)</td>
<td>35 (39.5)</td>
<td>33 (28.5)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>46 (12.7)</td>
<td>21 (24.1)</td>
<td>17 (14.9)</td>
<td></td>
</tr>
<tr>
<td>55+</td>
<td>111 (30.7)</td>
<td>14 (16.1)</td>
<td>42 (36.5)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>302 (83.7)</td>
<td>78 (89.7)</td>
<td>103 (89.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Other&lt;sup&gt;c&lt;/sup&gt;</td>
<td>52 (14.4)</td>
<td>8 (9.2)</td>
<td>11 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Provider level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>310 (85.9)</td>
<td>73 (83.9)</td>
<td>N/A</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>APP</td>
<td>51 (14.1)</td>
<td>14 (16.1)</td>
<td>115 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Earned license</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994 or earlier</td>
<td>122 (33.8)</td>
<td>11 (12.6)</td>
<td>18 (15.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1995-2004</td>
<td>103 (28.5)</td>
<td>24 (27.6)</td>
<td>38 (33.0)</td>
<td></td>
</tr>
<tr>
<td>2005 or later</td>
<td>136 (37.7)</td>
<td>52 (59.8)</td>
<td>59 (51.3)</td>
<td></td>
</tr>
<tr>
<td>Practice setting&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group/solo practice</td>
<td>259 (71.7)</td>
<td>50 (57.5)</td>
<td>59 (51.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital</td>
<td>116 (32.1)</td>
<td>18 (20.7)</td>
<td>34 (29.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Academic</td>
<td>59 (16.3)</td>
<td>22 (25.3)</td>
<td>19 (16.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Other&lt;sup&gt;e&lt;/sup&gt;</td>
<td>58 (16.1)</td>
<td>23 (26.4)</td>
<td>49 (42.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Medicaid patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to half</td>
<td>197 (54.6)</td>
<td>42 (48.3)</td>
<td>34 (29.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Half or more</td>
<td>160 (44.3)</td>
<td>45 (51.7)</td>
<td>81 (70.4)</td>
<td></td>
</tr>
<tr>
<td>Urban/rural location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large metro</td>
<td>121 (36.3)</td>
<td>20 (23.0)</td>
<td>40 (34.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Small metro</td>
<td>164 (45.4)</td>
<td>36 (41.4)</td>
<td>52 (45.2)</td>
<td></td>
</tr>
<tr>
<td>Micropolitan or rural</td>
<td>62 (17.2)</td>
<td>29 (33.3)</td>
<td>20 (17.4)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APP, advanced practice provider; N/A, not applicable.

<sup>a</sup>Many columns do not add to 100% due to data missingness.

<sup>b</sup>From chi-square test of homogeneity.

<sup>c</sup>Includes Hispanic, non-Hispanic black, non-Hispanic Asian, non-Hispanic American Indian/Alaska native, non-Hispanic Hawaiian /Pacific Islander, non-Hispanic “other.”

<sup>d</sup>Because this was a “check all that apply” item, multiple chi-square values and percentages exceed 100. “Other” includes Planned Parenthood, other family planning clinic, health maintenance organization or managed care organization (HMO), federally qualified health centers, and “other.”

<sup>e</sup>Includes Planned Parenthood, other family planning clinic, HMO/managed care, federally qualified health centers, and “other.”

<sup>f</sup>Only accounts for the first of up to 2 counties listed (N=103 listed a second county of practice).

contraception, specifically the utilization of LARC. Only those who answered “Yes” to the following specific questions were asked the final questions regarding progesterone supplementation, which generated the data analyzed for this study:

- “During the past 12 months, have you either provided prenatal care to patients or delivered babies?”
- “During the past 12 months, have you personally prescribed or made a referral for any of your pregnant patients to receive any type of progesterone supplementation to prevent preterm birth?”
(n=361), 15.5% (n=87) in family medicine, and 20.4% (n=115) as midwives.

Table 1 shows demographic and other characteristics of survey respondents by specialty. Age, provider level, year of licensure, urban-rural classification of practice location, and percentage of Medicaid patients varied by specialty (all \(P<.01\)). Family medicine providers tended to be younger and more likely to practice in micropolitan/rural areas than OB or midwife providers. OB providers were more likely to have been licensed in 1994 or earlier compared with family medicine and midwife providers, who were more likely to have been licensed in 2005 or later.

As shown in Table 2, 87.4% of OB providers (92.5% of physicians and 56.0% of APPs), 31.4% of family medicine providers, and 72.6% of midwife providers (all pairwise specialty differences \(P<.001\)) report prescribing at least 1 type of progesterone within the past 12 months for the prevention of preterm birth. An additional 4.9% of providers (n=27) reported having referred patients for progesterone for preterm birth prevention in the past year but did not personally prescribe it, with no differences by specialty. A greater proportion of midwife providers (10.6%) compared with those in OB (2.8%) referred patients for progesterone supplementation but did not prescribe it themselves (\(P=.0006\)). The total sample size among provider types is slightly lower than in Table 1 because 7 providers (4 OB, 1 family medicine, and 2 midwife) did not answer the question pertinent to the data in this table.

Among providers who reported prescribing at least 1 type of progesterone, the type prescribed differed by specialty. Most OB providers reported personally prescribing any 17OHP-C, versus family medicine and midwife providers (98.1% vs 77.8% and 80.5%, respectively; both \(P<.0001\)). In contrast, a greater proportion of family medicine and midwife providers reported prescribing oral progesterone than OB providers (40.7% and 24.4%, respectively, vs 13.1%; both \(P<.05\)). Overall, 62.5% of providers prescribed vaginal progesterone, with no differences by specialty (\(P=.61\)). (See Table 2.)

Makena was more commonly prescribed by OB providers than by family medicine and midwife providers (76.9% vs 51.9% and 52.4%; both \(P<.01\)); and the compounded formulation was prescribed more often by OB providers and midwives than by family medicine providers (64.4% and 63.4% vs 37.0%, respectively; both \(P<.05\)). Among providers who prescribed any 17OHP-C, about 90% of those in OB and family medicine reported that “most” or “almost all” of their patients completed the full course of therapy, compared to 77.3% of midwife prescribers.

Associations between urban-rural classification and prescription of vaginal and oral progesterone varied by specialty. Among OB and midwife providers, a greater proportion practicing in micropolitan/rural areas prescribed oral progesterone (29.6% and 53.3%) than those in small metropolitan areas (10.0% and 12.1%) and large metropolitan areas (9.5% and 24.2%; all \(P<.05\)). Among OB providers only, prescription of vaginal progesterone was more common in large metropolitan areas than micropolitan/rural areas (70.7% vs 46.3%, \(P=.002\)).

Figure 2 shows reported system- and patient-related barriers to the provision of 17OHP-C injections by provider specialty, among prescribers who responded (either positively or negatively) to at least 1 patient-related barriers item (97.4%) or 1 systems-related barriers item (95.5%). Medication cost was the most common systems-related barrier, reported by 29.9% of providers with no differences by specialty (\(P=.35\)). About one-quarter of OB (23.3%) and family medicine (24.0%) providers and one third of midwives (33.8%) reported challenges with preauthorization requirements. Though uncommon, safety concerns were more common among family medicine and midwife providers than OB providers (3% each vs 0.05%). Fewer than 5% of providers in every specialty group reported legal or efficacy concerns. Patient-level barriers were less common than system-level barriers. Overall, OB providers tended to report fewer patient-related barriers than family medicine and midwife providers.

**DISCUSSION**

We aimed to explore utilization and barriers to 17OHP-C amongst prenatal care providers in Wisconsin to identify opportunities to improve its utilization and impact rising preterm birth rates. Through a statewide survey of prenatal care providers, we found most OB and midwife providers report having prescribed or referred patients for progesterone to prevent preterm birth during the prior year, while family medicine providers were significantly less likely to have done so. Furthermore, there were significant differences in the both the formulation of 17OHP-C prescribed by the type of provider practice and their reliance on referral by provider specialty. In general, prescribing injectable progesterone was more common among OB and midwife providers than fami-
In general, injectable progesterone was prescribed more commonly by OB and midwife providers than family medicine; OB providers also prescribed Makena more often. A prior survey assessed types of progesterone prescribed by OB providers and, similar to our study, most were more comfortable prescribing Makena due to the FDA approval. In contrast, more family medicine providers and midwives prescribed oral progesterone, a difference potentially explained by a micropolitan or rural practice location. System-level barriers were reported most often among midwives, and few providers surveyed reported safety concerns.

The high rate of prescribing progesterone among OB providers in our survey is similar to the findings of other previous studies, in which 67% of board-certified maternal-fetal medicine specialists and 80% of obstetricians recommended progesterone use. Our study adds to this literature, providing estimates of use among prenatal care providers from other specialties. Most importantly, APPs from any specialty (56%) and family medicine (31.4%) were significantly less likely to prescribe progesterone for preterm birth prevention. This finding could be related to a perception that women with a prior preterm birth are “high risk” and elect to see or are referred to an OB provider to receive 17OHP-C, due to the typical practice pattern wherein most midwife and family medicine providers take “low-risk patients” in their practice.

To our knowledge, this is the first survey to assess choice of progesterone preparation by specialty. In general, injectable progesterone was prescribed more commonly by OB and midwife providers than family medicine; OB providers also prescribed Makena more often. A prior survey assessed types of progesterone prescribed by OB providers and, similar to our study, most were more comfortable prescribing Makena due to the FDA approval. We did not detect a difference in the reported prescription of vaginal progesterone across specialties; however, the prescription patterns suggest providers in large metropolitan areas were more likely to prescribe vaginal progesterone over other types. We did not assess the reasons providers prescribed vaginal progesterone or injectable progesterone. However, we speculate providers in large metropolitan areas may be more likely to prescribe vaginal progesterone due to underlying differences in the patient demographics, when patients present to care, differences in cervical length surveillance protocols and/or identification of a short cervix by ultrasound, lower health care costs, and ease of patient self-administration. The OB providers in our survey reported much less oral progesterone prescription, however family medicine providers were twice as likely to utilize oral progesterone. The efficacy of oral progesterone has not been well established and is considered inferior to the use of either intramuscular injections or vaginal formulations.

Our survey also aimed to understand the barriers providers face to implementing current recommendations for recurrent preterm birth prevention specifically associated with prescribing 17OHP-C. Patient- and system-related barriers were reported more frequently by family medicine and midwife providers than OB providers. Furthermore, providers practicing in rural areas, where there may be fewer health care resources, appear to choose alternative progesterone formulations. Together, these factors may lead providers to navigate the barriers as best as possible, despite being unable to follow best practice guidelines.

Similar to our findings, the most common reasons for failure to prescribe and/or administer progesterone reported in the literature are financial and logistical barriers, such as lack of insurance and/or medication cost. In addition, patient-level barriers, such as women presenting late to care, declining progesterone treatment, or compliance failure also may contribute to decreased utilization of 17OHP-C.
CONCLUSION

Our findings have important implications in identifying opportunities to improve 17OHP-C utilization for prevention of preterm birth, as we believe this is the first survey to compare the differences amongst OB, family medicine, and midwife prenatal care providers and the types of progesterone they prescribe. Despite prior studies and guidelines,10 adequate translation of 17OHP-C administration to all women at risk of recurrent preterm birth into clinical practice requires provider knowledge of recommendations as well as the reduction of provider-level, patient-level, and system-level barriers.

Our study suggests that further studies are needed to better understand decision-making patterns for prevention of preterm birth and to develop tools to assist providers in adhering to evidence-based guidelines when selecting treatment for women with a history of preterm birth. Educational initiatives to improve the translation of clinical evidence into practice with the support of clear guidelines and decision-support tools are essential in providing equitable and effective preterm birth prevention to all women.

Acknowledgements: We would like to acknowledge Emma Davis for her editing and revision work on the manuscript and Wisconsin providers for their contribution to the data.

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REFERENCES


Shivani Garg, MD, MS; Maria Mora Pinzon, MD, MS

ABSTRACT

Background: Secondhand smoke exposure can lead to serious health effects in vulnerable populations, including pregnant women. Studies report lower birth weight in pregnant women exposed to secondhand smoke.

Methods: We examined trends and risk factors of secondhand smoke exposure during pregnancy among nonsmoker pregnant women in Wisconsin from 2011 to 2016 using data extracted from the Wisconsin Interactive Statistics on Health (WISH) query system.

Results: There has been a decrease in overall trends of secondhand smoke exposure in pregnant women during the study period, with higher risk among pregnant teens, minority populations, and women with a lower education level.

Conclusion: To improve pregnancy and birth outcomes, future prospective and preventive studies should target groups with a higher risk of secondhand smoke exposure to quantify the risk and limit exposure.

INTRODUCTION

Secondhand smoke causes heart disease and lung cancer in adults and increased risk for sudden infant death syndrome, respiratory infections, asthma, and slowed lung growth in children. Studies also show that maternal exposure to secondhand smoke can adversely affect fetal growth and lead to poor birth outcomes. There is no risk-free level of secondhand smoke exposure, and the Surgeon General recommends that eliminating smoking in indoor spaces is the only way to fully protect nonsmokers from secondhand smoke.

Despite being aware of the impact of secondhand smoke exposure on health and birth outcomes, including low birth weight and fetal growth retardation, there are no effective strategies to eliminate indoor smoking and the impact of secondhand smoke exposure during pregnancy. Further, there are gaps in understanding sociodemographic risk factors related to secondhand smoke exposure in pregnant women in Wisconsin—information that can facilitate planning and directing targeted strategies to limit secondhand smoke exposure during pregnancy. Therefore, our study seeks to understand these trends and risk factors.

METHODS

We obtained data for nonsmoker pregnant women with and without secondhand smoke exposure in Wisconsin from 2011 to 2016 from the Wisconsin Interactive Statistics on Health (WISH) query system. Secondhand smoke exposure was defined as nonsmoker
pregnant women reporting living with a smoker. Sociodemographic data extracted for both groups included age, race, education, residence region, and birth data, including year of birth and adequacy of prenatal care. (Standard definitions for Kotelchuck index were used to define adequacy of prenatal care visits.)

We examined trends of secondhand smoke exposure in Wisconsin during the study period by mother’s year of delivery, region, age, race, education, and prenatal care. Additionally, we performed an age stratified analysis (<20 and ≥20 years) for race, prenatal care, and education level (defined as “completed high school or above” for ages 18-19 years and “some college or above” for ages ≥20 years). For each study variable, we compared the prevalence of secondhand smoke exposure using prevalence odds ratio (OR), standard errors, and 95% confidence intervals (CI). Microsoft excel was used to store data and perform calculations. Calculations were verified using R-3.4.1 software.

RESULTS
Overall Trend
From 2011 to 2016, the overall percentage of nonsmoker pregnant women in Wisconsin that were exposed to secondhand smoke decreased 2% from 2011 to 2015 and 10% from 2015 to 2016. There was a 65% difference in the rate of secondhand smoke exposure among pregnant women less than 20 years compared to those age 20 to 45 years (26% vs 9%). There were also higher rates of secondhand smoke exposure in minority populations, lower education levels, and the Northern region of Wisconsin (Table 1).

Risk Factors for Secondhand Smoke Exposure
During the study period, we found the odds of secondhand smoke exposure were 3.5 times higher in nonsmoker pregnant teens versus pregnant women 20 years or older (OR 3.5; 95% CI, 3.4-3.6). Among American Indian women, the odds of secondhand smoke exposure during pregnancy were 3.6 times higher than for white women (OR 3.9; 95% CI, 3.6-4.2). The yearly trend revealed a decrease in odds of secondhand smoke exposure in black and younger pregnant women. No significant change in odds of exposure was noted over time in American Indians and those with less education. (See Table 2.)

Age stratification revealed higher odds of secondhand smoke exposure among pregnant American Indian teens with less education. For pregnant women 20 years or older with less education, the odds of exposure were 2.4 times higher (OR 2.4; 95% CI, 2.3-2.5). Among black women age 20 years or older, the odds of exposure were 1.3 times higher compared to white women in the same age group (OR 1.3, 95% CI, 1.3-1.4); and despite receiving adequate prenatal care, pregnant teens reported 20% higher secondhand smoke exposure. (See Table 3.)

DISCUSSION
Our study shows that secondhand smoke exposure rates in nonsmoker pregnant women in Wisconsin decreased 2% from 2011 to 2015 and 10% from 2015 to 2016. However, we found that pregnant women from minority populations with a lower education level had higher risk of secondhand smoke exposure. There was no significant change in these trends over time. In addition, age stratification revealed that pregnant teens who were American Indian and who had less education had higher exposure to secondhand smoke, despite receiving adequate prenatal care.

This study highlights the sociodemographic risk factors of secondhand smoke exposure during pregnancy, which potentially could be targeted in future studies and preventive efforts, particularly for younger women. Further, our study underscores a need for future prospective studies to further examine the burden and impact of secondhand smoke exposure on pregnancy and fetal outcomes.

Wisconsin is one of the few states with persistently high ever-smoking prevalence in nonwhite populations. This could explain our finding of higher odds of secondhand smoke exposure during

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### Table 1. Trends in Secondhand Smoke Exposure Among Nonsmoker Pregnant Women by Sociodemographics and Birth Weight in Wisconsin, 2011-2016

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Nonsmoker Women Exposed to Secondhand Smoke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>5,702</td>
</tr>
<tr>
<td>2012</td>
<td>6,082</td>
</tr>
<tr>
<td>2013</td>
<td>5,883</td>
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<tr>
<td>2014</td>
<td>5,715</td>
</tr>
<tr>
<td>2015</td>
<td>5,708</td>
</tr>
<tr>
<td>2016</td>
<td>5,097</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>4,565</td>
</tr>
<tr>
<td>≥20 years</td>
<td>29,662</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White</td>
<td>22,938</td>
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<td>Black</td>
<td>3,984</td>
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<tr>
<td>Hispanic</td>
<td>3,493</td>
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<tr>
<td>Laotian or Hmong</td>
<td>1,243</td>
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<tr>
<td>Prenatal care</td>
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<tr>
<td>Adequate</td>
<td>22,157</td>
</tr>
<tr>
<td>Inadequate</td>
<td>6,009</td>
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<tr>
<td>Education level</td>
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<tr>
<td>8th grade or less</td>
<td>883</td>
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<tr>
<td>9th-12th grade/no diploma</td>
<td>4,633</td>
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<tr>
<td>High school graduate</td>
<td>12,678</td>
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<tr>
<td>Some college credit/no degree</td>
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<tr>
<td>Associate degree</td>
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<tr>
<td>Bachelor’s degree</td>
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<tr>
<td>Master’s degree</td>
<td>707</td>
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<tr>
<td>Doctorate or professional degree</td>
<td>148</td>
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<tr>
<td>Region</td>
<td></td>
</tr>
<tr>
<td>Southern</td>
<td>5,562</td>
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<tr>
<td>Southeastern</td>
<td>12,981</td>
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<tr>
<td>Northeastern</td>
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<tr>
<td>Western</td>
<td>4,279</td>
</tr>
<tr>
<td>Northern</td>
<td>2,906</td>
</tr>
</tbody>
</table>

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pregnancy in American Indian and black women and no significant change in trend in these groups over time.

Additionally, in 2017, the Centers for Disease Control and Prevention reported that American Indian teens had the highest birth rate (32.9%) compared to other racial groups.10 This may explain the significantly increased risk of secondhand smoke exposure during pregnancy in American Indian teens compared to other racial groups in our study.

Finally, education is one of the social determinants of health and socioeconomic status, which may indicate why less education was a predictor of higher exposure to secondhand smoke among pregnant women, irrespective of age.

There are limitations to this study. First, the data query from WISH resulted in aggregate data and not individual, patient-level data. Therefore, a multivariable analysis was difficult to perform. However, we tried to perform stratified and bivariate analysis to rule out confounding from common variables, for example, age and year of birth. Further, we had fewer American Indian pregnant women, which could have affected some analysis. Finally, our study is based on vital record information and we were unable to ascertain true exposure. Therefore, future prospective studies are required to understand predictors of secondhand exposure and plan preventive strategies to target predisposing risk factors.

CONCLUSION
This analysis reveals a decrease in overall trends of secondhand smoke exposure in nonsmoker pregnant women in Wisconsin from 2011 to 2016, with higher risk of exposure among teens, women from minority populations, and those with less education. Future prospective and preventive studies should target these populations to quantify risk and limit exposure to improve pregnancy and birth outcomes.

Acknowledgement: This work was conducted as part of a class project in the Population Health Program. We would like to thank Patrick Remington, MD, MPH, for his advice and guidance in designing and analyzing the data for this project.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

| Table 2. Prevalence Odds Ratio of Secondhand Smoke Exposure Among Nonsmoker Pregnant Women by Sociodemographic Variables and Health Care Provided in Wisconsin, 2011-2016 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age              | 20 years vs >20 years | Mean (95% CI)   | Mean (95% CI)   | Mean (95% CI)   | Mean (95% CI)   | Mean (95% CI)   |
| Race             | Black vs white  | 1.3 (1.1-1.5)   | 1.4 (1.3-1.6)   | 1.5 (1.4-1.6)   | 1.4 (1.3-1.5)   | 1.4 (1.3-1.5)   | 1.1 (1.1-1.3)   |
| American Indian vs white | 3.8 (3.1-4.7)   | 3.9 (3.2-4.9)   | 4.2 (3.4-5.1)   | 4.2 (3.4-5.2)   | 3.5 (2.9-4.4)   | 4.0 (3.2-5.0)   |
| Education        | <Degree vs degree | 3.6 (3.4-3.8)   | 3.6 (3.4-3.9)   | 3.6 (3.3-3.8)   | 4.0 (3.8-4.3)   | 3.9 (3.7-4.2)   | 3.6 (3.4-3.9)   |
| Prenatal care    | Adequate vs inadequate | 0.9 (0.8-0.9)   | 0.8 (0.9-1.0)   | 0.8 (0.8-0.9)   | 0.8 (0.7-0.8)   | 0.7 (0.7-0.8)   | 0.8 (0.8-0.9)   |

| Table 3. Prevalence Odds Ratio (95% CI) for Secondhand Smoke Exposure for Sociodemographic Variables After Age Stratification |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable         | <20 years       | >20 years       | OR CI           | OR CI           |
| Race             | Black vs white  | 0.5 (0.5-0.6)   | 1.3 (1.2-1.3)   |
| American Indian vs white | 1.9 (1.5-2.4)   | 0.4 (0.4-0.5)   |
| Education        | Lower level vs at level | 1.2 (1.1-1.3)   | 2.4 (2.3-2.5)   |
| Prenatal care    | Adequate vs inadequate | 1.2 (1.1-1.2)   | 0.9 (0.8-0.9)   |

Abbreviation: OR, odds ratio; CI, confidence interval.
Febrile Infection-Related Epilepsy Syndrome Treated Successfully With Anakinra in a 21-Year-Old Woman

Cecilia Westbrook, MD, PhD; Thanuja Subramaniam, MD; Ryan M. Seagren, PharmD; Erick Tarula, MD; Dominic Co, MD; Meghan Furstenberg-Knauff, APNP; Adam Wallace, MD; David Hsu, MD, PhD; Eric Payne, MD

ABSTRACT

Introduction: Febrile infection-related epilepsy syndrome (FIRES) is a syndrome of new-onset status epilepticus preceded by fever and highly refractory to treatment, thus resulting in high mortality and severe neurologic morbidity in surviving patients. Anakinra is an IL-1 receptor antagonist that has previously demonstrated efficacy in treating children with FIRES.

Case Presentation: A 21-year-old previously healthy woman presented with new-onset super-refractory status epilepticus following a febrile illness. This was subsequently diagnosed as FIRES after an extensive evaluation failed to identify an alternative etiology. The patient’s seizures were refractory to numerous antiepileptic drugs and immunomodulatory therapy. She was maintained under pharmacologic sedation for 31 days.

Management and Outcome: Anakinra was initiated on day 32 of her hospital stay, with swift and complete remission of her status epilepticus. Seizures ceased within 24 hours. The patient remains in remission with minimal side effects from the medication and no known long-term morbidity.

Discussion: Here we report what we believe is the second case of super-refractory status epilepticus due to FIRES responding to anakinra, and the first such case in an adult patient. Anakinra was well tolerated with few side effects. Our results are further evidence for the auto-inflammatory nature of FIRES and support the use of anakinra early in the treatment to prevent long-term sequelae.

INTRODUCTION

Status epilepticus is a neurological disorder familiar to most physicians working in emergency or intensive care settings. Most cases of status epilepticus are attributable to an identifiable neurologic insult and are amenable to commonly available anticonvulsants and supportive measures. When seizures are unresponsive to standard, adequately dosed benzodiazepines and a second line antiseizure medication (eg, valproic acid, levetiracetam, or fosphenytoin), the term refractory status epilepticus is used. When seizures continue for more than 24 hours despite the use of a continuous anesthetic infusion (eg, midazolam), a small subset of patients achieve super-refractory status epilepticus. This condition is exceptionally challenging to manage and confers an ominous prognosis.

New-onset refractory status epilepticus (NORSE) defines a syndrome of refractory status epilepticus occurring in an individual without active epilepsy and without a clear structural, toxic, or metabolic cause. A subcategory of NORSE, where seizure onset is preceded by a febrile prodrome, is termed febrile infection-related epilepsy syndrome (FIRES). (Other idiopathic new-onset status epilepticus and epilepsy syndromes have been described. A recent multinational consortium opted for subsuming all of these disorders under the NORSE/FIRES terminology.) Both the etiology and the optimal treatment of these disease entities remain unknown. Magnetic resonance imaging (MRI) is typically normal, though some frontal and temporal atrophy may occur over time. Evidence suggests an immune-mediated process, and thus, the mainstay has been immunomodulatory therapy including high-dose steroids, intravenous immunoglobulin (IVIG), and plasmapheresis. Evidence for these therapies remains sparse, however, and a plurality of patients do not achieve meaningful remission. Other treatments...
Figure 1. A Representative Seizure Captured in Patient Prior to Initiation of Anakinra

Abbreviation: EEG, electroencephalogram.
Quantitative EEG (qEEG) and raw EEG demonstrating a typical right posterior seizure. qEEG encompasses a 2-hour epoch. Trends include (in order, top down) rhythmicity spectrogram (left and right hemispheres), compressed spectral array (left and right hemispheres), asymmetry spectrogram, and amplitude integrated EEG. Individual seizures are marked with *. Raw EEG is shown from one of the seizures. EEG is time compressed to allow visualization of entire seizure. Seizure is characterized by rhythmic, sharply contoured, 4 Hz evolving to 8 Hz frequency, right posterior discharge.

have been tried, including tacrolimus, cyclophosphamide, rituximab, hypothemia, and the ketogenic diet. One particularly promising agent is anakinra, a recombinant form of the endogenously expressed IL-1 receptor antagonist (IL-1ra). There are now a handful of case reports of children with FIRES or other autoimmune status epilepticus syndromes being treated successfully with anakinra, indicating that IL-1 blockade can be effective for refractory seizures associated with neuroinflammation.

In this report, we present a case of a young woman with super-refractory status epilepticus, diagnosed as FIRES, which responded rapidly to anakinra despite initiation several weeks into the acute presentation. To our knowledge, this is the first reported case of FIRES successfully treated with anakinra in an adult. As in prior case studies, anakinra was rapidly effective and well-tolerated. This report provides additional evidence that anakinra may have benefit beyond traditional immunomodulatory therapies in new-onset super-refractory status epilepticus.

CASE PRESENTATION

A 21-year-old woman developed generalized tonic-clonic seizures after 1 week of intermittent subjective fevers. Her preceding illness was nonspecific, with headaches as the only localizing symptom. Her past medical history was significant only for migraine headaches, and family history was unknown to the patient. At the time of her illness, she was a college student also working as a cosmetologist. She was unmarried but in a long-term, stable relationship.

At the local hospital, her seizures did not respond to appropriately dosed benzodiazepines, levetiracetam, and lacosamide. She was intubated for airway protection, placed in pharmacologically induced coma, and transferred to an academic hospital after 3 days. On admission she was febrile to 100.5°F. She remained in a pharmacologically induced coma for the next 31 days.

Diagnostic Assessment

On admission, continuous electroencephalogram (EEG) monitoring revealed frequent electrographic seizures with onset over the right frontal and parietal regions (see Figure 1 for a representative example). Brain MRI revealed incidental developmental venous anomalies in the right frontal and parietal regions. C-reactive protein was elevated to 16.5 mg/dL (normal 0 – 1 mg/dL). Transaminases were initially elevated (ALT 155, AST 219 U/L) and resolved over the next 3 weeks. In an attempt to identify a surgical amenable seizure focus, an 18F-FDG PET scan was conducted on hospital day 22, revealing no hyper- or hypometabolic areas.

An extensive infectious workup was negative (see Box 1). Cerebrospinal fluid (CSF), blood, and urine cultures were negative at admission. A catheter-associated urinary tract infection developed later in her hospital stay.

Workup included computed tomography of the head, chest, abdomen, and pelvis, and transvaginal ultrasound. These studies were negative for neoplastic foci that might be associated with autoimmune encephalopathy. Repeated thyrotropin remained within normal limits. CSF studies showed glucose 46 mg/dL, total protein 49 mg/dL, 39 nucleated cells (94% lymphocytes), and 4 oligoclonal bands. Tests for cytokines were not collected and no sample was available to perform them after the fact. A CSF autoimmune encephalitis panel was negative (see Box 2). A serum autoimmune encephalopathy panel drawn later (on hospital day 15) was positive for contactin-associated protein-like 2 (CASPR2) antibodies and weakly positive for anti-glutamic acid decarboxylase (GAD; 0.08 nmol/L). This panel was drawn after 5 days of IVIG.
administration, which complicates interpretation. Notably, repeat serum studies 3 months after hospital discharge were negative for all tested antibodies. Electromyography and nerve conduction study performed 11 days after initiation of anakinra demonstrated findings of mild critical illness myopathy but was otherwise normal. C-reactive protein normalized to <1 mg/dL within 3 weeks, suggesting resolution of systemic inflammation.

Consideration was given to a diagnosis of macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), which is a primary autoinflammatory disorder that can cause CNS disturbance and seizure. Ferritin (29 ng/mL) and soluble IL-2 receptor α (800 units/mL) were both normal, which is inconsistent with MAS/HLH, although these were not tested until 2 weeks after anakinra was started.

**Therapy**

The patient was initiated on antiepileptic drugs (AED) and anesthetic medications that were adjusted to maintain her EEG in a burst-suppression pattern. This was accomplished with combinations of pentobarbital, propofol, and midazolam for approximately 3 weeks, after which pentobarbital was cross-titrated to ketamine for 1 more week. Repeated attempts to wean anesthesia intermittently precipitated an EEG pattern of generalized periodic discharges with increasing frequency concerning for seizure and later more defined focal electrographic seizures. AEDs were gradually added until her final regimen consisted of 2,500 mg levetiracetam twice daily, 200 mg lacosamide twice daily, 20 mg clobazam twice daily, 130 mg phenobarbital 3 times daily, and perampanel 8 mg daily. On this regimen she still had EEG-confirmed subclinical focal seizures when anesthesia was weaned.

In addition to her sedation and AED regimen, the patient received early immunomodulatory therapy. Specifically, she received IV methylprednisolone for 5 days starting on hospital day 8, followed by a prednisone taper; IVIG for 5 days starting on hospital day 11; and plasmapheresis treatments on hospital days 18, 20, 22, 24, and 26. She did not demonstrate appreciable clinical response throughout this time.

Following apparent therapeutic failure of first-line immunomodulatory therapies, the patient was initiated on anakinra on hospital day 32 at 100 mg 3 times daily. Total cessation of seizures was achieved within 24 hours of initiating anakinra, and pharmacologic coma was weaned off within another 24 hours. Ketogenic therapy also was initiated on hospital day 34, but she did not achieve ketosis and this therapy was discontinued on hospital day 45. Her mental status began to improve quickly; she began following commands and moving her limbs within 3 days of cessation of sedation and was fully oriented by 10 days (hospital day 42). She showed swift motor recovery, ambulating independently by hospital day 67. Anakinra was reduced to 100 mg twice daily on hospital day 48 and then to 100 mg once daily on hospital day 64. She progressed through physical therapy and rehabilitation and was discharged within 6 weeks (hospital day 73) on a scheduled taper of phenobarbital, levetiracetam, clobazam, and lacosamide.

At 6-month outpatient follow-up, she described regaining baseline physical and cognitive abilities, and returning to work and college courses. She has not experienced further seizures. She does not report side effects from the medication and has not been neutropenic. Tapering of antiseizure medications is expected to be complete within 1 year. Anakinra will be continued for 1 year, at which time discontinuation will be discussed. Repeat imaging and

---

**Box 1. Infectious Workup for Patient**

**Viruses**
- Herpes simplex virus 1 and 2
- Epstein-Barr virus
- Cytomegalovirus
- Varicella zoster virus
- HIV 1 and 2
- Hepatitis A (prior immunity)
- Hepatitis B
- Hepatitis C
- Arbovirus
- West Nile virus
- Mumps (prior immunity)
- Rubeola
- Respiratory virus panel
  - Influenza A Subtypes H1 and H3
  - Influenza B
  - Parainfluenza 1, 2, and 3
  - Rhinovirus
  - Enterovirus
  - Metapneumovirus
  - RSV subtypes A and B
  - Lymphocytic choriomeningitis virus

**Bacteria and Other Organisms**
- Tuberculosis
- Syphilis
- Cryptococcus
- Lyme disease
- Ehrlichiosis
- Anaplasma
- Coccioidioides
- Histoplasma
- Blastomycosis

**Box 2. Paraneoplastic Antibodies Tested in Patient**

**Cerebrospinal Fluid**
- NMDA-R Ab
- Neuronal (V-G) K+ Channel Ab
- LGIT-IgG
- CASPR2 IgG
- GAD65 Ab
- GABA-B-R Ab
- AMPA-R Ab
- ANNA type 1
- ANNA type 2
- ANNA type 3
- AGNA type 1
- PCA type 1
- PCA type 2
- PCA-Tr
- Amphiphysin Ab
- CRMP-5-IgG

**Serum**
- NMDA-R Ab
- Neuronal (V-G) K+ Channel Ab
- LGIT-IgG
- CASPR2 IgG (positive)
- GAD65 Ab (positive)
- GABA-B-R Ab
- AMPA-R Ab
- ANNA type 1
- ANNA type 2
- ANNA type 3
- AGNA type 1
- PCA type 1
- PCA type 2
- PCA-Tr
- Amphiphysin Ab
- N-type calcium channel Ab
- P/Q-type calcium channel
- Acetylcholine receptor (muscle) binding Ab
- ACHR ganglionic neuronal Ab
- CRMP-5-IgG
EGG are planned once she has discontinued her AEDs. (The full timeline of the patient’s treatment can be found in Figure 2.)

**DISCUSSION**

In this report we have described a previously healthy 21-year-old woman who developed new-onset super-refractory status epilepticus consistent with febrile infection-related epilepsy syndrome (FIRES). Despite multiple treatment failures, she responded swiftly to the recombinant IL-1 receptor antagonist anakinra and appears to have achieved complete remission with minimal residual effects. Although it is possible that her clinical response was attributable to the delayed effects of another immunomodulatory therapy, the sudden and dramatic nature of her recovery would be unusual, and the timeline is more compelling for a response to anakinra. This is the second published report of FIRES responding to anakinra, and the first in an adult patient, which is notable due to the substantial morbidity and mortality of this syndrome in adult patients.

The success of anakinra in this patient’s treatment is valuable not only for future management of this disorder, but also in suggesting an autoinflammatory rather than autoimmune mechanism for the status epilepticus syndromes NORSE and FIRES. The majority of cases are not associated with known autoantibodies, which argues against a classic autoimmune disorder in which antigen-specific T or B cells mediate neuronal dysfunction. Instead, the previously reported association with elevations in pro-inflammatory cytokines that resolved with administration of anakinra instead support the assertion that FIRES represents an autoinflammatory disorder. Autoinflammatory disorders are more recently described conditions in which the innate immune system is directly activated without the need for a specific antigen. From a clinical standpoint, autoinflammatory disorders respond to therapies targeting innate immune system cytokines such as IL-1 and may not respond to more familiar autoimmune therapies such as IVIG, tacrolimus, or even steroids. Thus, the responsiveness of FIRES to anakinra is highly suggestive of an IL-1-driven inflammatory cascade as a key pathogenic mechanism.
CONCLUSION
This is the first case report of an adult patient with acute onset super-refractory status epilepticus presenting immediately after a febrile illness (ie, FIRES) whose seizures did not respond to conventional immunotherapy but were abolished shortly after initiating anakinra. She recovered to her premorbid baseline. To put this case into broader perspective, the super-refractory status epilepticus syndromes NORSE and FIRES are rare but devastating conditions that are challenging to treat. Standard immunomodulatory modalities are the mainstays of therapy but are frequently unsuccessful. This case report and others provide increasing evidence for the benefit of novel immunomodulatory therapies targeting the innate immune system, particularly anakinra, in NORSE and FIRES. Because of its safety and the high risk of permanent neurologic sequelae from these disorders, we recommend considering initiating anakinra early in the course of treatment for adults as well as children presenting with new-onset super-refractory status epilepticus.

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REFERENCES
CASE REPORT

Triple Diagnosis of Crohn’s Disease, Celiac Disease, and Eosinophilic Esophagitis in a Child With Siderius-Hamel Syndrome

Rajni Ahlawat, MD; Nirzar S. Parikh, MD; Ajay Jhaveri, MBBS, DNB

ABSTRACT

Siderius-Hamel syndrome is a rare condition characterized by intellectual disability and distinct facial features. Crohn’s disease-related eosinophilic esophagitis (EoE) has been reported; however, an association between celiac disease and EoE remains controversial. We present a case of a child with Siderius-Hamel syndrome who had characteristic findings of all these conditions—Crohn’s disease, celiac disease, and EoE—an occurrence that to our knowledge has not been reported previously. The purpose of this report is to make physicians aware of this rare occurrence, so that it can be kept in mind while evaluating a patient with Siderius-Hamel syndrome presenting with gastrointestinal complaints.

INTRODUCTION

Siderius-Hamel or Siderius X-linked mental retardation syndrome is a rare condition and only a few families with this condition have been described in the literature.1-6 Crohn’s disease-related eosinophilic esophagitis (EoE) has been reported; however, the association between celiac disease and EoE remains controversial.7,8 There is an increased risk of autoimmune conditions, such as Crohn’s disease, ulcerative colitis, and celiac disease, in patients with EoE, with possible shared genetic etiology between ulcerative colitis and EoE.9 We describe the first reported case of a child with Siderius-Hamel syndrome, who had characteristic findings of all 3 conditions—an occurrence that, to our knowledge, has not been reported previously.

CASE REPORT

An 11-year-old white boy with Siderius-Hamel syndrome presented to the gastroenterology clinic for abdominal pain and constipation for 1 month. He was diagnosed with Siderius-Hamel syndrome at 5 years of age based on mild intellectual disability; developmental delay; dysmorphic features, including arched eyebrows, hypertelorism, broad nasal bridge, and thin upper lip; and identified PHF8 mutation on the genetic test. For gastrointestinal symptoms, he was treated with laxatives and had improved stool frequency and consistency, though abdominal pain persisted. Two weeks later, he developed nonbloody diarrhea, which persisted after discontinuing the laxatives. Pertinent negatives include dysphagia, odynophagia, food impaction, hematochezia, and weight loss or growth problems.

Laboratory investigations showed abnormal celiac serology with elevated tissue transglutaminase IgA of 16.8 U/mL (normal range 0-14.9 U/ml), antigliadin IgA of 72.2 U/ml (normal range 0-14.9 U/ml), antigliadin IgG of 27.2 U/ml (normal range 0-14.9 U/ml) and anti-endomysial IgA of 1:10 (normal < 1:10). IgA level was normal at 185 mg/dL (normal range 50-330 mg/dL). Complete blood count, comprehensive metabolic panel, and inflammatory markers also were normal. Stool infectious studies were negative. An esophagogastroduodenoscopy (EGD) showed mild linear furrowing of the esophagus (Figure 1a) and duodenal bulb erythema. Colonoscopy was remarkable for mild erythema, erosions, and exudates in the terminal ileum. The colon and cecum appeared grossly normal. EGD biopsies detected up to 20 eosinophils per high-power field (HPF) in both the distal and proximal esophagus (Figure 1b, 1c) as well as duodenum with increased intraepithelial lymphocytes (approximately 39/100 enterocytes) and mild villous blunting (Figure 2a). Colonoscopy biopsies showed chronic active

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ileitis and chronic active colitis with a focal granuloma (Figure 2b), confirming the diagnosis of Crohn’s disease. Computed tomography enterography revealed a normal small bowel.

The patient was started on a strict gluten-free diet and treated with oral prednisone 40 mg daily and subcutaneous methotrexate 15 mg weekly, due to the patient’s inability to swallow pills. Steroids were gradually tapered off over a period of 6 weeks. To establish the diagnosis of EoE, a follow-up EGD almost 3 months after treatment with high-dose proton pump inhibitor (omeprazole 20 mg twice daily) was performed, which showed worsening esophagitis (marked linear furrowing and mucosal edema) (Figure 3a). Biopsies revealed > 30 eosinophils per HPF in both distal and proximal esophagus (Figure 3b, 3c), findings consistent with EoE. Duodenal biopsies showed improved intraepithelial lymphocytes (approximately 21/100 enterocytes) and no villous atrophy. In addition to gluten-free diet, a milk and soy elimination diet was recommended. To identify additional food allergens, the patient was referred to the Allergy and Immunology Department. Rapid allergo sorbent test was negative. Skin prick test could not be performed as the patient was noncooperative. At 3-month follow-up, abdominal pain and diarrhea resolved while on injectable methotrexate and gluten-free diet. Follow-up celiac serology was normal. Stool calprotectin was normal at 22.0 mcg/g, although baseline stool calprotectin at initial diagnosis was not done. The patient had poor adherence to the elimination diet; therefore, a third EGD to assess response to treatment with dairy and soy elimination diet for EoE was not done until family reported dietary adherence for at least 3 months. A third EGD was done 9 months after the second EGD and showed improved linear furrowing in the distal esophagus with normal appearing proximal esophagus. Biopsies revealed up to 25 eosinophils per HPF and up to 15 eosinophils per HPF in distal and proximal esophagus, respectively. Duodenal biopsies showed worsening duodenitis (increased intraepithelial lymphocytosis and villous blunting, which was not seen on the second EGD). We suspect that the finding on third EGD could be related to poor adherence to the dairy and soy elimination, and gluten-free diet. The patient continues to remain under our follow-up, and the importance of strict compliance to the dietary elimination has been discussed.

DISCUSSION

Celiac disease is a Th1-mediated autoimmune disease triggered by ingestion of food containing gluten in genetically susceptible individuals.10 EoE is a Th2-mediated inflammatory disorder triggered by exposure to dietary allergens leading to the invasion of the esophageal mucosa by eosinophils, T lymphocytes and mast cells.11 Celiac disease and EoE are 2 immune-mediated conditions that affect the upper gastrointestinal tract, in response to dietary triggers. Elimination of food triggers can lead to clinical as well as histological improvement in both conditions.12 The coexistence of EoE and celiac disease in the same patient was first described by Shah et al in 2006.13 In recent years, multiple studies have assessed whether an association exists between celiac disease and EoE in children, with variable results.7,8 Most recently, Hommeida, et al, found no increased risk of EoE in children with Crohn’s disease in the largest cohort study and meta-analysis to date.14

Crohn’s disease is a predominantly Th1-mediated-mediated chronic inflammatory condition of the gastrointestinal tract. Patients with celiac disease have an increased risk of developing Crohn’s disease compared to the general population.15 Active Crohn’s disease can be associated with increased esophageal eosinophilia,16 therefore it was not clear at first if it was primary EoE or Crohn’s-related esophageal eosinophilia. However, based on the distinct endoscopic appearance and finding of esophageal eosinophilia, which worsened on follow-up EGD despite the use of proton pump inhibitors, primary EoE appeared more likely. It is difficult to conclude if persistent esophageal eosinophilia despite treatment of Crohn’s disease is due to primary EoE, as clinical implications of mucosal eosinophils in inflammatory bowel disease are still being researched.17

It has been shown that patients with Crohn’s disease can have...
low positive levels for anti-tissue transglutaminase (tTG) antibodies; however, antiendomysial antibodies are reported to be detectable only in celiac disease.18,19 Our patient also had mildly elevated tTG IgA; however, the presence of abnormal anti-endomysial IgA, antgliadin IgG and IgA, and histopathology findings, all went in favor of celiac disease. Celiac genetics also could be considered in this patient; however, based on the above-mentioned findings, clinical response and normalization of celiac serology, as well as histological improvement on gluten-free diet, confirmed the diagnosis of celiac disease. Therefore, celiac genetics was not determined necessary.

Siderius X-linked mental retardation syndrome is characterized by cleft lip, cleft palate, and distinctive facial features, including long face, sloping forehead, broad nasal bridge, supraorbital bridge, and upslanting palpebral fissures, and is caused by mutation in PHF8, which encodes a chromatin remodeling protein with putative transcription factor activity.1-5 Thus far, not a single case of Siderius X-linked mental retardation syndrome with this combination of autoimmune conditions has been reported. Since the PHF8 gene is being linked with regulation of immune activity, it is possible that modification of the PHF8 influenced the development of immune-mediated diseases, rather than our finding being a mere coincidence.

CONCLUSION

This case highlights a rare occurrence between 3 distinct gastrointestinal conditions—Crohn’s disease, eosinophilic esophagitis, and celiac disease—in a patient with Siderius X-linked mental retardation syndrome. Additional studies are necessary to assess the relationships between the development of these conditions and PHF8 activity.

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REFERENCES


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<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCW Survivorship Symposium</td>
<td>11/22/19</td>
</tr>
<tr>
<td>Updates in General Surgery Symposium</td>
<td>12/7/19</td>
</tr>
<tr>
<td>MCW Pancreatic Cancer Clinical Symposium</td>
<td>1/31/20</td>
</tr>
<tr>
<td>The Milwaukee Aortic Symposium</td>
<td>3/20/20</td>
</tr>
<tr>
<td>Midwest Regional Trauma &amp; Acute Care Surgery Symposium</td>
<td>6/1/20 - 6/3/20</td>
</tr>
<tr>
<td>Central Surgical Association Annual Meeting</td>
<td>6/4/20 - 6/6/20</td>
</tr>
<tr>
<td>Surgical Oncology Symposium</td>
<td>10/22/20 - 10/23/20</td>
</tr>
</tbody>
</table>

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Academic Medicine in the United States has an enormous impact on the health and well-being of US citizens through directly caring for patients, developing the knowledge that changes lives through new discoveries and research, preparing the next generation of physicians and scientists, and engaging with communities.

In Wisconsin, we are fortunate to have two academic health systems linked to the two medical schools in the state: the School of Medicine at the Medical College of Wisconsin (MCW) and the University of Wisconsin School of Medicine and Public Health. Together, these institutions have trained the majority of physicians who practice in Wisconsin! These Wisconsin-based medical schools cumulatively brought in approximately $297.4 million in federal funding in 2017-2018 for biomedical research to bring new discoveries to the state’s patients—providing hope for those with the most complex medical conditions and creating substantial positive economic impact for Wisconsin.

In addition to serving as dean of the Medical College of Wisconsin School of Medicine, I am fortunate to have another role nationally, as the incoming chair of the Board of Directors for the Association of American Medical Colleges (AAMC) as of mid-November 2019. The AAMC serves and leads the academic medicine community to improve the health of all and focuses on transforming health care in four primary mission areas: medical education; patient care; medical research; and diversity, inclusion, and equity in health care. The AAMC and its member medical schools, teaching hospitals, and academic societies are committed to being part of the solution to improve the nation’s health care system, and to leading the change that improves health.

The AAMC’s imperative to improve the health for all is what most attracted me to service in this organization. It also is a mission that is significant to all physicians in the United States and Wisconsin—whether currently part of academic medicine or simply associated with it through their years as a medical student and trainee in graduate medical education. As noted on the AAMC website: “The AAMC collaborates with its members and their multisector community partners to make progress towards health equity, address public health crises, and ensure that all people can get the care they need from a diverse, inclusive, and culturally responsive physician workforce. Through this collaboration, the AAMC leads and serves the academic medicine community to improve the health of all.”

The AAMC recently named David Skorton, MD, as its new president and chief executive officer, following a distinguished career in government, higher education, and medicine. In my upcoming role as chair of the AAMC board, I will work with Dr Skorton and the staff and board of the AAMC to develop a strategic plan for the organization to guide its areas of emphasis. This is an important time for medicine in general—and for academic medicine in particular—as we work collectively to improve the health of our nation and to tackle the many changes that are moving forward in our profession.

Although strategic planning for the AAMC under its new leadership is in its earliest phases, this organization has been at the forefront of working with medical schools on physician education, advocating for the importance of biomedical research for our society, and supporting teaching hospitals and academic health systems in their educational and clinical missions to care for patients with the most complex health problems.

I am hopeful for the future of the AAMC’s strategic plan and its outcomes—and feel extremely fortunate to participate in its creation. I would be most happy to hear from readers of the *WMJ* should you have particular thoughts related to this important process. I look forward to further sharing with anyone who is interested in the process and the eventual outcome of this work. Please feel free to reach out to me at jkerschner@mcw.edu.

**REFERENCES**

The development of solid organ and bone marrow transplantation has been considered among the most important medical advances in the last half of the 20th century. Solid organ and bone marrow transplant programs at the University of Wisconsin School of Medicine and Public Health (SMPH) and UW Health started more than 50 years ago. Since then, our solid organ transplant program has performed over 16,000 transplants, making it the largest such program in the Midwest and one of the largest and most successful in the nation. The underpinnings of both programs are their scientific accomplishments in immunology and their highly collaborative, innovative approach. A recent example is the endeavor to perform kidney transplants without the lifelong need for antirejection medications, referred to as immunological tolerance.

The discovery of immune chimerism and its link to immunological tolerance observed by pioneering investigators at UW-Madison several decades ago are transforming organ and bone marrow transplantation.

Dr Kaufman is the Ray D. Owen Professor of Surgery and chair of the Division of Transplantation, Department of Surgery, University of Wisconsin School of Medicine and Public Health (UW SMPH); Dr Hematti is a professor of medicine at the UW SMPH and director of the Clinical Hematopoietic Cell Processing Laboratory and Apheresis and Bone Marrow Collection Center at UW Health; Dr Golden is the dean of the UW School of Medicine and Public Health and vice chancellor for medical affairs, University of Wisconsin-Madison.

The success in providing a long life for a solid organ transplant recipient depends on avoiding transplant rejection. There are two ways to avoid immune rejection of a transplanted organ:

- Through perfect tissue matching between identical twins, an uncommon situation in which the recipient and donor share the same tissue HLA and other antigens. In this case, no immunosuppressive drugs are required because all HLA antigens match, and there is no destructive immune response that needs to be suppressed. The next best matching situations are between
HLA-identical siblings and between siblings who share one HLA allele, called a haplo-match. HLA-matched transplants, nevertheless, still require immunosuppression due to the existence of numerous minor transplantation antigens.

• Through the use of drugs that suppress the recipient’s immune response, thereby preventing organ rejection. Immunosuppressive medications—which are required for the rest of the patient’s life—prevent a destructive allo-immune event and allow the transplanted organ to survive despite differences in HLA and/or minor antigens between the recipient and the donor. These drugs have revolutionized the field of transplantation and saved hundreds of thousands of lives that otherwise would have been lost due to failure of a vital organ. Unfortunately, all available immunosuppressive drugs increase susceptibility to infection and have other side effects that often cause severe morbidity.

The ability to perform solid organ transplants without the life-long need for immunosuppression requires the induction of transplant-specific tolerance in the recipient. The UW Health and SMPH solid organ and bone marrow transplant programs are putting their combined efforts into new basic science and clinical research studies that aim to produce immunological tolerance in kidney transplant recipients, thus eliminating the need for anti-rejection medications. This approach requires creation in the recipient of a dual immune system consisting of the patient’s own and that of the organ donor. The coexistence of dual immune systems is called “immune chimerism.”

The UW Health clinical tolerance induction protocol involves a combined kidney and hematopoietic cell transplant between sibling donor and recipient pairs. The new program is led collaboratively by two of the authors, Drs Dixon B. Kaufman and Peiman Hematti.

This team-oriented clinical research program also involves collaborators in the Department of Human Oncology, including Kristin Bradley, MD, and the Division of Transplantation’s Clinical Trials Unit.

Such tolerance-induction studies using combined kidney and bone marrow transplantation strategies were initiated in October 2018 and are being conducted in two groups of living-related kidney transplant patients: (1) recipients of an HLA-identical kidney transplant between siblings and (2) recipients of a living donor transplant that is matched among two and five HLA antigens.

The discovery of immune chimerism and its link to immunological tolerance observed by pioneering investigators at UW-Madison several decades ago are transforming organ and bone marrow transplantation. Building on the past, we look forward to the future impact of the current, exciting clinical studies of immunosuppression-free transplantation.
Index to Advertisers

All of Us ................................................................. 107
Gimbel, Reilly, Guerin & Brown LLP ................................. 107
Health Partners .................................................................. 111
Hurley Burish, S.C. .......................................................... 147
Medical College of Wisconsin, Department of Family & Community Medicine .................................................. 111
Medical College of Wisconsin Department of Surgery .......... 144
PNC Bank ........................................................................... IFC
ProAssurance Group .......................................................... BC
US Army ............................................................................. 148
University of Wisconsin-Madison Interprofessional Continuing Education Partnership ................................. 112, 147
Wisconsin Department of Health Services ......................... 108
WisMed Assure .................................................................... IBC

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