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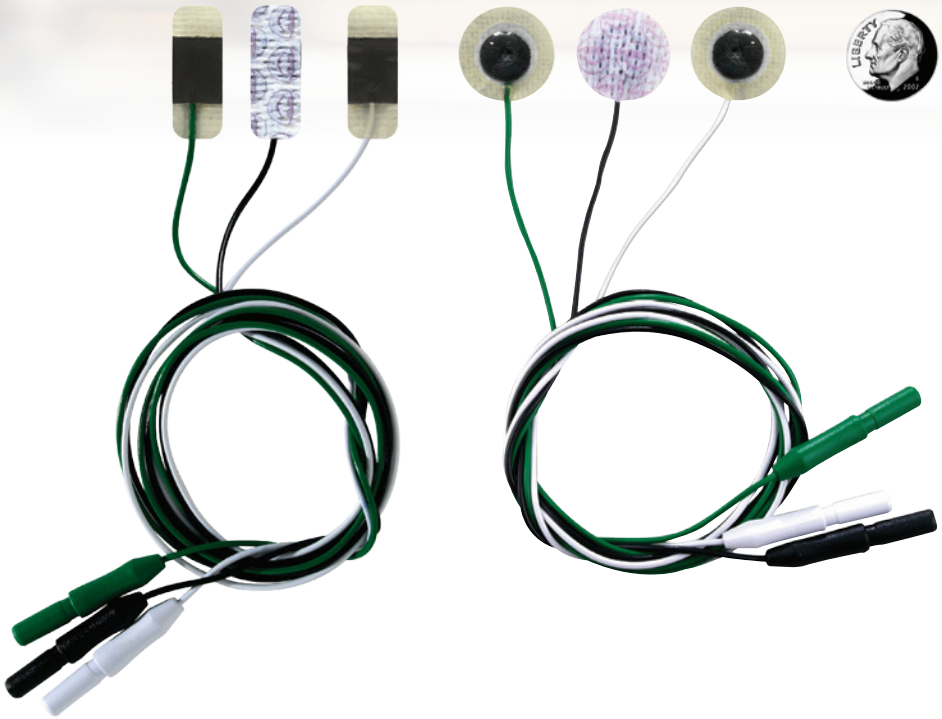

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Groundbreaking Treatment for Newborn

In a groundbreaking medical achievement, doctors in Philadelphia have successfully treated a newborn, K.J. Muldoon, with a customized CRISPR gene-editing therapy for a rare and fatal genetic disorder called severe carbamoyl phosphate synthetase 1 (CPS1) deficiency. Diagnosed shortly after birth, K.J. lacked a crucial liver enzyme that helps remove toxic ammonia from the body. Without prompt intervention, he would have required a liver transplant. Physicians Dr Rebecca Ahrens-Nicklas and Dr Kiran Musunuru rapidly developed and secured regulatory approval for a tailored CRISPR treatment in just six months—a process that typically takes years. Administered via lipid nanoparticles to target the liver, the therapy led to remarkable improvements in K.J.'s health. While it's early to declare a cure, the infant now shows significant weight gain and reduced medication needs. Experts say this case demonstrates the potential of personalized gene-editing therapies for treating ultrarare conditions and could serve as a model for future individualized medical treatments. K.J. is expected to return home soon, symbolizing a hopeful future for gene-editing and personalized medicine. This successful application of CRISPR technology underscores the transformative potential of gene editing in treating rare genetic conditions. It also highlights the importance of continued research and collaboration in the field of personalized medicine. For those interested in exploring the science and ethics of gene editing further, the book CRISPR People: The Science and Ethics of Editing Humans offers an in-depth look into the subject.

Dräger expands neonatal care portfolio with BiliPredics software solution

Dräger is expanding its neonatal care portfolio with the introduction of BiliPredics, a predictive software solution from NeoPredics designed to forecast dynamic progression of bilirubin. By leveraging a clinically validated algorithm, BiliPredics can enable healthcare professionals to anticipate bilirubin progression up to 60 hours in advance, helping to support timely and informed clinical decisions. Key benefits include: **Enhanced Discharge Planning:** Supports clinicians to help reduce unnecessary treatments, tests, and extended hospital stays through predictive insights into bilirubin progression. **Data-Driven Decision Making:** Utilizes an extensive database of over 50,000 individual bilirubin measurements of close to 10,000 newborns with a total of about 100,000 individual patient characteristics. **Integrated Jaundice Management:** Helps provide a streamlined pathway for screening, monitoring, and treating neonatal jaundice. Neonatal jaundice affects approximately 50% of all newborns and up to 80% of premature babies.[1] BiliPredics offers a proactive approach to jaundice management by forecasting bilirubin progression over 30, 48, or 60 hours. The web-based application presents this data in an accessible dashboard, helping to enable clinicians to implement preventive measures and reduce the risk of complications. BiliPredics requires only a few clinical parameters to generate comprehensive insights. It aligns with established guidelines, including the 2022 AAP Hyperbilirubinemia Guideline, and can integrate with electronic medical records (EMR) to display patient data within the dashboard. The system presents bilirubin trends through comprehensible curves, helping to allow for real-time assessment and intervention. "Through our partnership with NeoPredics, we are expanding our offering with an innovative digital solution that strengthens our position as a leader in jaundice management," said Harald Kneuer, director of neonatal care at Dräger. "By combining Dräger's market expertise with NeoPredics' advanced predictive analytics, we are providing healthcare professionals with powerful tools to improve patient outcomes while managing costs." NeoPredics CEO, Thorsten Waloschek, echoed this sentiment: "Our collaboration with Dräger is a significant milestone in advancing neonatal care. Together, we are bridging innovative technology

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Cover: French: Le nouveau-né by André Gill (1840–1885). The image is public domain.

and clinical expertise to address critical challenges in jaundice management worldwide." Dräger's neonatal care portfolio includes solutions for both screening and treatment of neonatal jaundice. The Dräger Jaundice Meter JM-105 offers non-invasive, rapid bilirubin measurement, while the BiliLux Phototherapy Light provides effective LED-based phototherapy for jaundice treatment. This approach helps ensure adherence to the latest guidelines, reinforcing the concept of "phototherapy as a drug" with precise irradiance dosing.

Preterm Birth Affects Adult Relationships, Fertility

Preterm birth has lasting effects into adulthood, with very premature individuals struggling to form romantic relationships and having fewer children, according to the Bavarian Longitudinal Study. Published in *JAMA Network Open*, the study, led by Miranda Kit-Yi Wong, MSocSc, from the Department of Psychology, University of Warwick, Coventry, England, tracked very premature infants born since 1985, now aged 34-35 years, and compared them with full-term individuals. The researchers analyzed 414 participants, including 212 individuals who very premature (< 32 weeks' gestation) or very low birth weight (VLBW) (< 1500 g) and 202 full-term individuals. The results showed that by the age of 34-35 years, 56.4% of full-term individuals had children compared with only 35.8% of premature individuals. Previous cross-sectional studies have suggested a link between a history of preterm birth and fertility. "The Bavarian Longitudinal Study, however, has been ongoing for nearly 40 years. The cohort of newborns included back then is now 34- to 35-years old and has been evaluated 10 times," said Peter Bartmann, MD, PhD, co–project leader and professor at the University Hospital Bonn in Bonn, Germany. For Bartmann, it is important to emphasize that the project only concerns those born very early and very small and by no means all premature babies. "This is only a small group of those affected, about 1.0%-1.5% of births," he said. Key factors such as gender and socioeconomic status influenced outcomes, but the link between preterm birth and fertility persisted. However, this association was no longer significant after adjusting for partnership status. "Individuals with a history of preterm birth find it harder to establish a partnership, which in turn reduces the likelihood of having children," Bartmann explained. Premature individuals who formed partnerships had children at rates comparable with those of full-term individuals. Why do premature individuals struggle to form partnerships? "Studies show that this group develops a different personality structure," Bartmann noted. "They are more introverted, take fewer risks, face bullying in school, have fewer friends, and struggle to form social connections."

Nirsevimab Cuts Hospitalisation Risk in Infant Bronchiolitis

Immunisation with nirsevimab reduced bronchiolitis-related hospitalisations among infants younger than 3 months who visited the emergency department (ED), according to a new study. Nirsevimab also reduced respiratory syncytial virus (RSV) positivity and paediatric intensive care unit (PICU) admissions. Researchers conducted a retrospective study across six paediatric EDs in France, including 739 infants younger than 3 months with a clinical diagnosis of bronchiolitis during the 2023-2024 RSV epidemic season. The primary outcome was hospitalisation after an ED visit, and the secondary outcomes included PICU admissions and RSV positivity. Subgroup analyses considered prematurity, age groups, and social deprivation, as assessed by the French Deprivation Index. The analysis was adjusted for age, sex, centre, visit week, comorbidities, bronchiolitis history, gestational age, and deprivation score. Nirsevimab showed 53.5% adjusted effectiveness in reducing bronchiolitis-related hospitalisations among infants after ED visits (95% CI, 34.1-67.3; $P < .001$). Hospitalisation rates were 51% in immunised infants and 69% in non-immunised infants. Nirsevimab showed 51.1% (95% CI, 10.7-74.3) and 79.6% (95% CI, 68.0-87.1) effectiveness in reducing PICU admissions and RSV positivity, respectively. Immunisation showed a consistent protective effect in preterm infants, neonates, and deprived groups, though statistical significance was not reached in smaller subgroups. "These findings support the widespread use of nirsevimab to prevent severe respiratory infections caused by RSV in young infants, highlighting its potential to substantially reduce the healthcare burden associated with bronchiolitis," the authors wrote. The study was led by Alexis Marouk, SAMU 93 - SMUR - Emergency Department, Avicenne Hospital, Public Assistance Hospitals Paris, Bobigny, France. It was published online on March 5, 2025, in the *European Journal of Pediatrics*.

Tocolytics Do Not Improve Neonatal Outcomes in Preterm Birth

The contraction inhibitor atosiban (Tractocile) was no better than placebo for neonatal outcomes in the context of threatened preterm birth, the investigators in the multicenter, randomized, placebo-controlled assessment of perinatal outcome after specific tocolysis in early labor (APOSTEL) 8 superiority trial reported in *The Lancet*. "The most important result of our study, that tocolytic drugs do not improve neonatal outcome when administered above 30 weeks of gestation, was unexpected," the study coauthor Larissa I. van der Windt, MD, an obstetrician

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and PhD candidate at Amsterdam University Medical Center in Amsterdam, the Netherlands, said. "The primary goal of tocolysis should not be prolongation of pregnancy but improvement of neonatal outcomes." Between December 2017 and July 2023, a total of 755 adult women at 26 Dutch, English, and Irish hospitals were randomized; 752 were included in the intention-to-treat analysis. The primary endpoint was a composite of adverse neonatal outcomes. These included perinatal mortality up to 28 days postpartum, which included bronchopulmonary dysplasia, periventricular leukomalacia > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis > Bell's stage 1, retinopathy of prematurity > grade 2 or needing laser therapy, and culture-proven sepsis. The primary outcome occurred in 37/449 (8.2%) infants in the atosiban group and 40/435 (9.2%) in the placebo group (relative risk [RR] 0.90; 95% CI, 0.58-1.40). Three (0.7%) and four (0.9%) infants died in the two groups, respectively (RR, 0.73; 95% CI, 0.16- 3.23). All deaths were deemed unlikely to be related to the study drug, and maternal adverse events did not differ between groups. In the atosiban group, significantly more pregnancies were prolonged beyond 48 hours than in the placebo group (292/375, 78% vs 261/377, 69%; RR, 1.13; 95% CI, 1.03-1.23). There were 15 (4%) planned cesarean sections in the atosiban group vs 29 (8%) in the placebo group (RR, 0.52, 95% CI, 0.28-0.95). The overall cesarean section rate, however, was similar in both groups (RR, 0.90; 95% CI, 0.69-1.16). Other secondary neonatal and maternal outcomes did not significantly differ between groups. There were 17 serious adverse events in the atosiban group and 12 in the placebo group, again, not considered treatment related. Although atosiban itself is not approved in the United States, tocolytic drugs have long been part of standard care, primarily based on studies investigating surrogate outcomes such as increasing gestational age and are often used off-label to prevent premature labor. In the APOSTEL 3 trial, the tocolytics nifedipine and atosiban were equally effective in prolonging pregnancy, but nifedipine showed a nonsignificant twofold increase in neonatal mortality. "When we looked into the evidence for whether these drugs are actually associated with better neonatal outcomes, we found no study demonstrated a positive effect of tocolytic therapy," van der Windt said. "We felt it was time to investigate these drugs with the proper primary outcome because tocolytic drugs should be given with the purpose of improving neonatal outcomes." Van der Windt questioned the advisability of inhibiting contractions in the setting of preterm labor since most women affected go into preterm labor for reasons such as infection or placental problems. "In this setting, it might not be the best option to try to inhibit contractions." In her opinion, further research should primarily focus on preventive therapies/interventions for preterm birth.

Doula Care Boosts Vaginal Birth Success Rates and Postpartum Follow-Ups

Doula care was associated with 15-34 more vaginal births after cesarean per 100 deliveries and increased exclusive breastfeeding rates by 20%. Support from doulas also reduced preterm births by 3-4 cases per 100 deliveries, with benefits consistent across race and insurance status. Researchers conducted a retrospective cohort study of 17,831 deliveries from January 2021 to December 2022 at a single institution, analyzing outcomes for 486 patients who received doula care compared with 17,345 patients who did not. Analysis included maternal outcomes (cesarean delivery, vaginal birth after cesarean, gestational hypertension, preeclampsia, or postpartum emergency department visits) and neonatal outcomes (neonatal intensive care unit admission, breastfeeding, or preterm delivery). Investigators used multiple methods including multivariate logistic regression and conditional regressions with propensity scores to generate appropriate comparison populations, accounting for targeted outreach to high-risk patients. Patients receiving doula care showed significantly higher rates of vaginal birth after cesarean (adjusted risk difference [ARD], 15.6; 95% CI, 3.8-27.4) and increased postpartum office visit attendance (ARD, 5.4; 95% CI, 1.4-9.5). Exclusive breastfeeding rates were 22% higher among patients with doula support (adjusted risk ratio, 1.22; 95% CI, 1.07-1.38). Doula care was associated with fewer preterm births (ARD, −3.8; 95% CI, −6.1 to −1.5) per 100 deliveries. Benefits of doula support remained consistent regardless of patient race or insurance status, as demonstrated across multiple analytical approaches. "Although doulas are posited to have a significant impact on numerous maternal and neonatal outcomes and to decrease racial disparities, research that quantifies these effects is limited…The impact of doula support on the general population and the influence of race and payor status have been largely unexplored," wrote the authors of the study.

30-Year Boom in NICU Capacity Hasn't Lowered Mortality

The number of neonatologists in the United States has grown 227% in the last three decades and the number of neonatal intensive care unit (NICU) beds has grown 48%, but those increases appear to have had no effect on lowering newborn mortality rates, said authors of a new study. Authors, led by Gwenyth M. Gasper, MS, with the Dartmouth Institute for Health Policy and Clinical Practice, in Hanover, New Hampshire, wrote that "although NICU care is highly effective in the treatment of serious newborn illness, recent growth in the number of total neonatologists and NICU beds has occurred independent of need and is not associated with newborn mortality at either the individual or the regional level." Findings were published on March 24 in *JAMA Pediatrics*. The researchers concluded that, "The benefits and costs of current NICU capacity and further growth warrant clinical and policy scrutiny." However, an expert not involved with the study said the numbers don't tell the whole story of NICU care. The study points out that from 1991 to 2020, the number of neonatologists increased from 0.44 to 1.44 per 1000 live births (227%) and NICU beds per 1000 live births increased from 5.43 to 8.02 (48%). Over the same period, mortality decreased from 3.87 to 2.21 (−43%) and 180-day mortality decreased from 6.27 to 3.19 (−49%) per 1000 live births. However, there was no meaningful correlation between change in regional capacity (neonatologists: r, −0.12; 95% CI, −0.25 to 0.00; NICU beds: r, −0.07; 95% CI, −0.19 to 0.06) and change in regional neonatal mortality. The lack of an association held up even with stratification by gestational age, maternal education, and maternal race or ethnicity and restriction of the infant population to very low birthweight newborns, which the authors pointed out is "a uniquely high-risk population." NICU care has been highly effective in the treatment of serious newborn illness and has led to dramatic reductions in neonatal morbidity. Success stimulated growth, but the growth was uneven by region, the authors noted. "Regions with higher perinatal risk are not more likely to experience higher capacity growth. Furthermore, despite its association with NICU utilization, higher NICU bed capacity is not reliably associated with lower risk of inpatient mortality or short-term post discharge outcomes, suggesting possible oversupply in some regions," the authors wrote.

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Early Developmental Challenges: Speech, Language, and Swallowing in Neonates With Tracheostomies

Megan Quinn, MSN, PNP-PC

Improvement in resuscitation in the perinatal and neonatal period has led to increased survival rates for infants,[1] some of whom have been born with medical complexities that will necessitate tracheostomy. As management of these critically ill infants evolves, tracheostomy discussion and placement must evolve as well.[1] Neonatal tracheostomy has always been a large proportion of pediatric tracheostomies performed overall. Up to 60% of pediatric tracheotomies are performed within the first year of life and approximately half of the neonatal patients admitted to the NICU requiring a tracheostomy are less than 37 weeks gestation.[1] There are multiple indications that could lead to a neonate requiring tracheostomy. Even though tracheostomy placement is often safe, there are still risks associated. Risks can range from delays in development to life threatening complications. While there is data regarding life-threatening complications, more infants are surviving into childhood and beyond.[2] There is limited research regarding risk of speech, language, and swallowing impairments related to tracheostomy in the neonatal population. Further research could help identify opportunities to reduce these impairments.

Indications

There are many diagnoses that could require tracheostomy placement in the neonatal population. Many databases have shown an increase in tracheostomy placement in neonates, likely due to increased survival rates.[1] Tracheostomies are commonly placed in neonates who require prolonged ventilation, have an upper airway obstruction, or to help facilitate slow ventilator weaning.[3,4]

Bronchopulmonary dysplasia (BPD), a common complication for premature infants, is a diagnosis that could require a neonate to undergo tracheostomy.[1] As patient outcomes in this population are improving, tracheostomies in the neonatal BPD population have increased.[1] Upper airway obstruction is a primary indication for tracheostomy in the neonatal population.[2] There are multiple underlying diagnoses that can contribute to upper airway obstruction, including Pierre Robins syndrome, craniofacial abnormalities, laryngomalacia, hemangiomas, or infection.[2] Neurological deficits that disrupt the infant's ability to breathe successfully, cough, or protect their airway are also indications for tracheostomy.[2] Neonatal tracheostomy can be indicated for various reasons, which complicates the assessment and intervention of developmental milestones.

Megan Quinn is a Clinical Educator at Atos Medical Inc. Prior to her role at Atos Medical, Ms Quinn worked in the Pediatric Intensive Care Unit and the Pediatric Palliative Care Team at a Midwestern Children's Hospital.

Complications

Pediatric tracheostomy has a complication rate of up to 60%.[1] Complications can occur both during surgery as well as in the postoperative period. These include tube occlusion, accidental decannulation, hemorrhage, and skin breakdown.[1] Preterm infants (less than 37 weeks gestation) have a higher risk of complications after tracheostomy placement compared to term infants. These preterm infants were found to have higher risk of pneumonia and sepsis.[1]

There are short-term complications that can occur after tracheostomy placement. These complications include bleeding, necrosis, mucus plugging, infection, and ulceration.[3] Accidental decannulation can also occur, however with close monitoring and assessment, this risk can be minimized.[3] Multiple factors are often involved in long-term complications.[3] An improperly positioned or an inappropriately sized tube can lead to ulceration or erosion that can contribute to formation of a tracheoesophageal fistula (TEF), which can be life threatening.[3] There are many other long-term complications that can form over time. As neonatal patients with tracheostomy live longer, the risk of long-term complications increases. It's important to note that both short-term and long-term risks can have negative impacts on development.

Tracheostomy Effect on Swallowing, Speech, and Language

Swallowing

Swallowing is often difficult for patients at any age with a tracheostomy. It has been reported that up to 87% of patients with tracheostomy have difficulty swallowing.[5] The reason for this is multifactorial. The physical tracheostomy tube can prevent the normal movement of the larynx, which makes it difficult to protect the airway during swallowing.[5] Larynx movement can be slowed after tracheostomy placement, which can contribute to delayed initiation of natural swallow response.[5] Additionally, there can be impairments in the glottic closure reflex and decreased ability to create glottic pressure, which can make it more difficult to swallow safely.[4] As reviewed, patients with a tracheostomy often have multiple medical conditions, some of which also contribute to dysphagia.[5] Additionally, the prolonged hospitalization that accompanies tracheostomy placement in neonates negatively affects swallowing.[5]

Figure 1. Tracoe Mini tracheostomy tube with obturator.

Cuffed tracheostomy tubes are shown to negatively affect swallowing in infants with a tracheostomy tube.[2] This is due to the cuff preventing full hyolaryngeal elevation (this is the upward and forward movement of the hyoid bone and larynx) as well as potential impingement on the esophagus.[2] Using a cuffless tracheostomy tube may minimize the risk of impingement on the cuffless esophagus and incomplete hyolaryngeal elevation. There are various cuffless tracheostomy tube options available for neonates, including Tracoe Silcosoft and Tracoe Mini.

The neonatal population, some of whom might have been intubated since birth, could have had difficulty with swallowing even prior to tracheostomy placement. The suck-swallow-breathe coordination is not fully developed until 37 weeks gestation and there are patients in the NICU who have not reached this gestational age.[4] This population may experience disrupted development of swallow coordination, which can be adversely affected if a tracheostomy is performed before 37 weeks gestational age. In general, neonatal patients with tracheostomy placement have difficulty taking PO even upon discharge. One study showed that 57% of infants with a tracheostomy tube were discharged with some type of supplemental tube feeding method.[3]

Dysphagia in the neonatal tracheostomy population has not been well studied. However, there is research in pediatrics that could be a guiding force for future neonatal research. Within the pediatric population, speaking valve use has been shown to improve sensation in the upper airway and contributes to improved subglottic pressure building to help with rehabilitation of swallow.[4] Though one-way speaking valves are often used in pediatrics, they might not be as well tolerated in the neonatal population due to their smaller airways and inability to fully exhale around the tracheostomy tube. Speaking valves that allow for titration of resistance could be a valuable tool in the population. One speaking valve that is gaining popularity in the pediatric population is the Tracoe PhonAssist I speaking valve. This speaking valve allows for partial exhalation through the tracheostomy tube while also allowing airflow through the upper airway. This adjustable resistance can be customized to each patient.

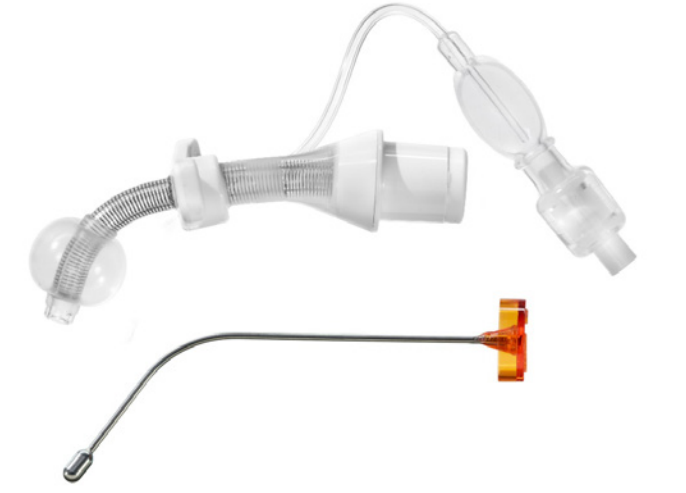

Figure 2. Tracoe Silcosoft cuffed tracheostomy tube with proximal extension and obturator.

In addition to speaking valves, options such as different bottles, different nipples (which can help reduce flow speed), and/or thickened fluids are modifiers that can be trialed.[5] While thickened feeds have been shown to decrease episodes of regurgitation (which can be seen in neonates with GERD even without tracheostomy), there is risk of increased fatigue and prolonged transition to oral feeding seen when thickeners are used.[2] Positioning changes, jaw and/or cheek support, and tactile stimulation have also been utilized to modify feeding for infants with tracheostomy.[2] These are common methods in NICUs and can be tailored to each patient.[2]

Figure 3. Tracoe PhonAssist I.

Even though there is concern about swallowing after tracheostomy placement, one study found that 73% of pediatric patients with a tracheostomy were approved to take oral feeds in some capacity after surgery.[5] Having this data in the neonatal population could be helpful not only for families but for the medical team as well. Difficulty swallowing is an important possible sequalae of tracheostomy placement that should be studied in the neonatal population as well.

Speech and Language

Neonates who require a tracheostomy often have compromise of their upper airway from an extremely young age, potentially even from birth. This compromise can lead to significant delays in the maturation of the upper airway and the physiological role it plays in the body.[5] Due to the lack of upper airway airflow, it is not surprising to learn that speech delay is common in this population.[5]

In a neonate, speech patterns, language, and voicing are developing during their time in the NICU. During the first three months of life in a typical baby, infants learn to make cooing sounds as well as formulate cries that vary based on what the infant needs.[6] However, neonates who have a tracheostomy are not able to make audible sounds which could lead to a delay in speech and language development.

As neonates with a tracheostomy are often in the hospital for long periods of time, they could miss further milestones, such as making gurgling sounds, showing likes and dislikes via sound, and babbling, all of which develop between 3-6 months

of age.[6] These are all important for normal speech and language development.

Many adult and pediatric patients with tracheostomy tubes use one-way speaking valves to facilitate voicing. Speaking valve use in neonates for audible voicing is not well studied. In pediatrics, their airway is rapidly growing and changing, even with a stable airway this growth must be accounted for when determining speaking valve options.[5] As mentioned previously, a speaking valve, such as the Tracoe PhonAssist I with a customization option could play a role in the ability produce audible sounds. Audible sounds are important precursors to speech and language development. Additionally, sounds like crying, cooing, and babbling are beneficial for the family and caregiver bonding.

While tracheostomy in the neonatal population is not new, there remains much to learn about speech, language, and swallowing development. Studies aimed at therapeutic approaches to optimize these important developmental milestones would be extremely beneficial. Existing tools used in the pediatric population have yet to be applied in neonatal care. Speech, language, and swallowing are critical developmental milestones that warrant closer study.

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Reducing Pain in the NICU: A Quality Improvement Initiative at Woman's Hospital

Mark Schorr, RRT, Cindy Voelker, MD, FAAP, Meagan Dexter, RNC-NICN

Introduction

As infants of increasingly low gestational ages are resuscitated, NICU care has accordingly adapted to meet the needs of these fragile patients. Improvements in perinatology have led to the survival of infants with gestational ages as low as 22 weeks. For patients this small, the road ahead is long and difficult.

Life-sustaining procedures are frequently needed to help these babies survive. These procedures are often painful and can be more harmful to the developing brain of the extremely low birth weight infant. Research shows that premature infants are significantly affected by repeated exposures to pain.[1,2] An increasing body of research has demonstrated that pain during a NICU stay can lead to long-term negative developmental consequences.[3-8]

One such painful procedure is the all-too-common blood draw. Although necessary, these sticks are often repeated frequently throughout a NICU stay. This procedure can be done for a variety of reasons; one of the highest drivers is blood gases.[9]

CO_2 in the NICU

The need for visibility to a patient's CO_2 is critical in the NICU. CO_2 is a major factor in cerebral blood flow regulation.[10] High, low, and fluctuating CO_2 levels have all been associated with increased risk for intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and other negative outcomes.[11-16]

As a result, NICU teams must pay close attention to these values when they are balancing the protection of both the neonatal brain and fragile, underdeveloped lungs. Targeting optimal ventilation and maintaining consistent levels of cerebral blood flow are both primary goals — and CO_2 is at the heart of both.

Blood draws are a way to monitor these values. However, other methods of monitoring CO_2 can also provide information.

Transcutaneous CO_2 monitoring is a noninvasive, continuous method of measuring $PaCO_2$. A sensor, placed on the skin, gently warms the skin to allow CO_2 to diffuse through the skin. A measurable reaction takes place to estimate the arterial CO_2 levels of the patient. This offers providers a continuous value, rather than the point-in-time measurement that blood draws represent.

Mark Schorr, Cindy Voelker and Meagan Dexter are with Woman's Hospital, Baton Rouge, LA.

At-A-Glance: Woman's Hospital Level III NICU

- 84 beds
- >1,000 annual admissions
- 300 NICU nurses
- 44 respiratory therapists

Adopting transcutaneous monitoring at Woman's Hospital

In October 2021, our NICU director expressed a strong desire to introduce transcutaneous CO_2 ($tcPCO_2$) monitoring to the NICU. Initially, there was some hesitancy from the respiratory team — the result of an unsuccessful attempt to introduce the technology here in the past.

However, this time was more successful, likely as a result of a more strategic, educational introduction for staff. During previous attempts, staff distrust of the technology was tied to inaccuracies in correlation; however, when our team began using contact gel and reviewing correlations with blood gases, staff buy-in improved.

For the first 18 months, the team (and crucially neonatologist) continued to build trust in the technology. Meanwhile, team leaders began to discuss how to standardize usage. During this time, our staff kept monitors in use at all times; deciding *which* patients to use it on became the central issue that leadership sought to solve.

In June 2022, the Quality Improvement Team in the NICU decided, as part of our process improvement, to target

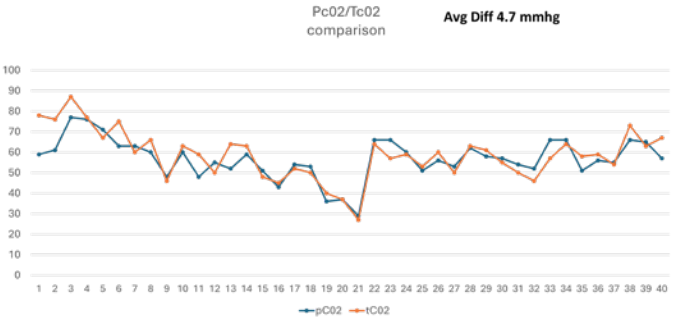
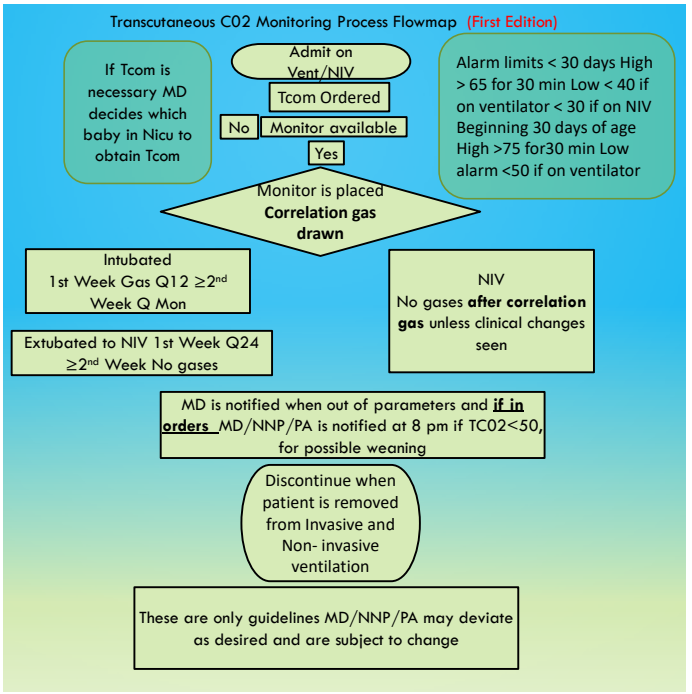


Figure 1.



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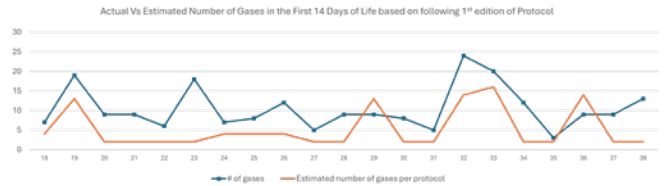

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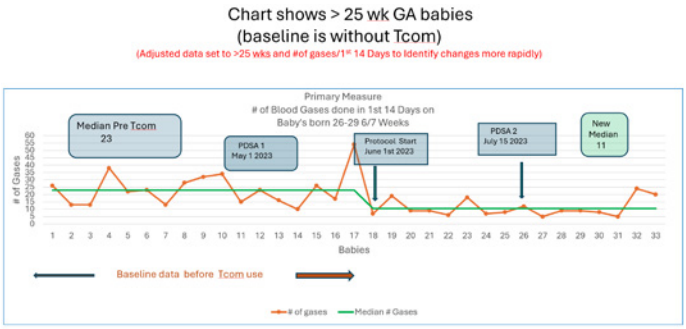


Figure 4.

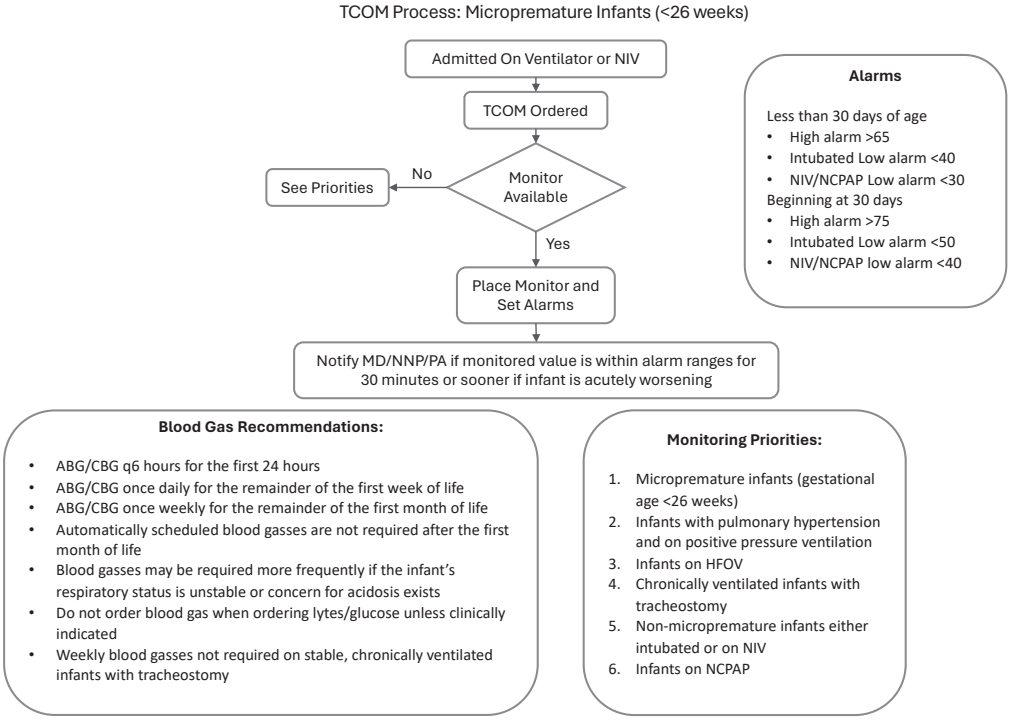
minimizing noxious stimuli that neonates experienced in our NICU. This project would demonstrate whether the use of $tcPCO_2$ monitoring would have an effect on the number of blood gases drawn from NICU patients while they were receiving respiratory support.

The goal of the project would be to reduce the number of gases performed, thereby reducing exposure to pain and, ultimately, reducing long-term harmful effects to the developing brains of our patients.

Quality improvement initiative: Reducing pain and noxious stimuli

This project was undertaken in steps, in order to support usage and encourage trust in the devices. To start, the Quality Improvement Team created a PCO_2/$tcPCO_2$ comparison chart, showing data from the NICU's patients to demonstrate correlation. Data was collected from a variety of patients, varying in conditions and gestational ages (Figure 1).

Starting in January 2023, a focus group of nurses and respiratory therapists convened, with the goal of setting a baseline for staff understanding of transcutaneous CO_2 technology. Based on results from the focus group, an educational process was



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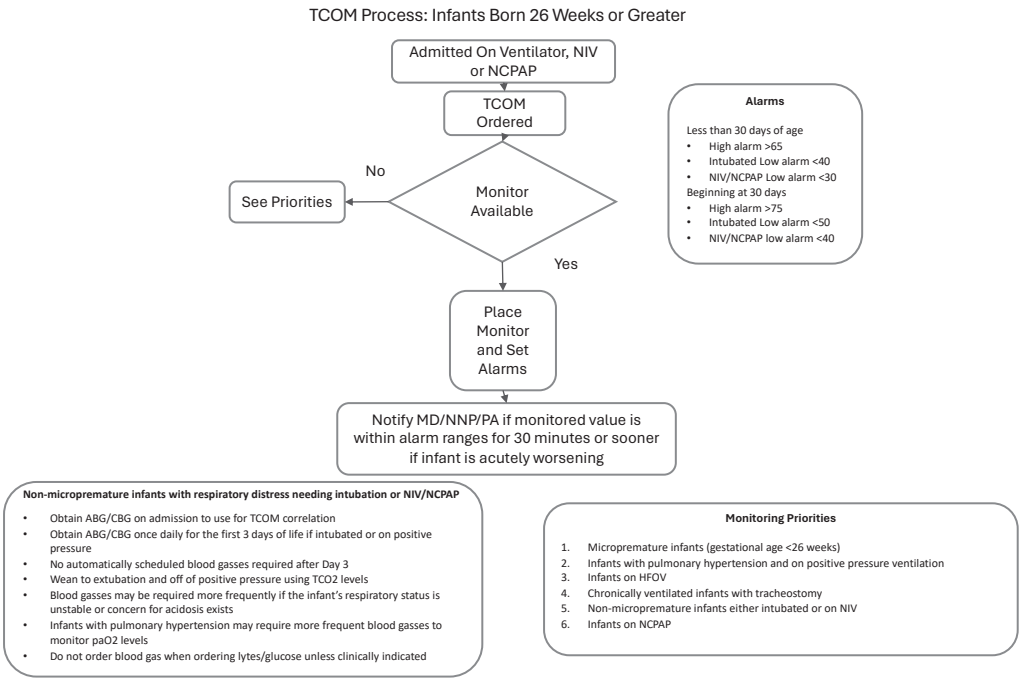

Figure 6.

developed to strengthen understanding. This was done through bedside educational in-services, provided by clinical specialists with both respiratory and nursing backgrounds.

Then, in June 2023, the first standardized protocol was implemented. This was created to guide ventilator management decisions and determine when blood gases would be drawn (Figure 2).

We narrowed the scope to examine the first 14 days of ventilation and decided to limit the population to 26-29 6/7 weeks GA to get a more homogenous set of data and to identify changes more quickly. These parameters were used for the first three months of implementing the standard protocol.

Data collected during this time is reflected in Figures 3 and 4. There was a clear demonstration of reduced blood gases — the result of simply placing monitors on the unit and using them consistently.

However, the Quality Improvement Team sought to adjust the process to further improve the protocol. Review of the process revealed that adherence to the protocol was not always occurring, and further analysis showed that opportunities to further reduce pain were being missed.

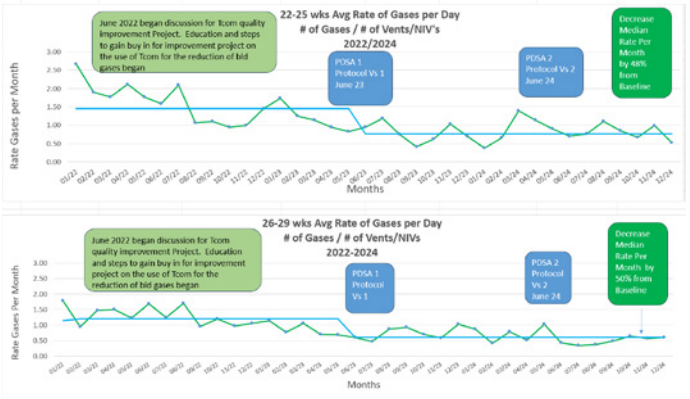

Figure 7.

Therefore, the team reconvened to adjust the protocol (Figures 5 and 6). Version 2 was released, accompanied by staff education and data-tracking efforts. This second phase of data collection began in June 2024.

Lessons and surprises

Today, $tcPCO_2$ is widely used in our unit. As soon as extremely premature infants (as young as 22 weeks) arrives in the NICU, a $tcPCO_2$ sensor is immediately placed.

Having continuous CO_2 values provides a crucial level of visibility that our unit needs to facilitate our care when managing these tiny infants. Combined with pulse oximetry, $tcPCO_2$ offers us a vital tool in patient evaluation — real-time visibility offers our team a complete picture of our patient's respiratory status.

Although our respiratory team is in charge of $tcPCO_2$ monitoring, the process of implementation revealed a surprising amount of interest and investment from our nursing team as well. Nurses are educated on the value of our $tcPCO_2$ monitors and are often active participants in monitoring. They are even able to use those values to advocate for fewer blood draws when possible.

Our data collection efforts are ongoing, but the results from this quality improvement initiative are promising. The number of average blood gases per day has decreased significantly over the course of the last two years, in premature infants from 22-25 weeks and 26-29 weeks GA (Figure 7). The first year of usage has resulted in a more than 50% reduction in blood draws performed.

Conclusion

Our team continues to look for ways to improve our processes and knowledge to impact patient care. Our work in reducing blood draws is ongoing, as we aim to prevent long-term negative outcomes for our patients. Transcutaneous CO_2 monitoring has been a valuable tool in achieving this goal and remains a vital

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WHITEPAPER

Balancing Brain & Lung Protection in the NICU with Transcutaneous CO2 Monitoring

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The very same ventilatory support that can help keep CO_2 within safe ranges for brain protection can also damage the lungs without careful consideration. Failing to deliver enough volume can result in derecruitment and atelectasis. Delivering too much risks overdistension and volutrauma.

In this way, the brain and the lungs are in constant tension – what protects one can harm the other. To prioritize lung protection and avoid potentially harmful airway pressures, respiratory teams may employ a strategy of permissive hypercapnia, which can help keep plateau pressures within a safe range, but could put the brain at risk. Prioritizing the brain may require increased ventilator settings that damage the lungs. In these scenarios continuous visibility to CO_2 can be a powerful, even vital, tool to balance both priorities.

Continuous CO_2 monitoring can be a valuable tool when care teams employ permissive hypercapnia, as it can allow them to keep a close eye on how the patient is responding and to react quickly to unexpected changes or spikes.

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resource for our NICU. In our hospital, use of transcutaneous monitoring has led to the reduction of blood draws and allowed us to have a simple, continuous visibility into a patient's respiratory condition.

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Cracking the Diagnostic Code Early: How WGS is Transforming Newborn Care

Shruti Sureshkumar, MSc, GC

Every moment matters when a newborn is critically ill. The wait for a diagnosis might seem never-ending to families and medical professionals who are familiar with unexplained symptoms in the first few days or weeks of life. Traditional newborn screening programs, while effective for certain conditions, have limitations — many rare and early-onset genetic disorders go undetected until symptoms become severe. This diagnostic delay not only impacts outcomes but also puts an emotional and financial strain on families.

Why is whole genome sequencing diagnostically superior?

Whole Genome Sequencing (WGS), through technologies like Next-Generation Sequencing, is redefining the future of newborn diagnostics. Unlike traditional methods, NGS provides a comprehensive look at a baby's genetic makeup, enabling clinicians to diagnose rare monogenic disorders within days (Mittal et al., 2022). The diagnostic sensitivity of WGS is higher than that of other genetic testing techniques, including exome sequencing (Lionel et al., 2017). Paediatric patients in critical condition have shown the greatest therapeutic utility of WGS, impacting health care management better outcomes and notable cost savings (Balciuniene et al., 2023).

WGS is replacing the use of panels in preventive and precision medicine. It helps in screening for specific disease risks, expanded carrier testing, pharmacogenomic variants (Pan et al., 2022). As sequencing costs continue to decrease, WGS is emerging as a feasible option for widespread population screening, especially for newborn screening (NBS) (Perkins et al., 2018) (Bick et al., 2022). Studies also suggest that the integration of WGS with traditional NBS can be considered. Large publicly and privately funded initiatives are examining the practicality, clinical benefits, and cost-effectiveness of using WGS for the babies in NICU (Kingsmore et al., 2022) (UK National Screening Committee, 2021) (Ceyhan-Birsoy et al., 2019). Traditional diagnostic methods, including targeted

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genetic testing, biochemical analysis can take weeks to months leading to "diagnostic odyssey" or no diagnosis at all. The term "diagnostic odyssey" is defined as the long, often fruitless journey many families undergo while seeking a diagnosis for their child's condition. For infants in the NICU, this delay can lead to worsening outcomes or even death due to the rapid progression of their condition.

WGS decodes nearly all of an individual's genome, providing a comprehensive picture of their genetic information. Ultrarapid whole genome sequencing (urWGS) goes a step further by optimizing the entire process by maintaining the accuracy and delivering the results in a fraction of time when compared to the traditional methods. The ability to perform the entire process from sequencing to analysis in a matter of days is a game-changer of how genetic conditions are diagnosed.

A retrospective study showed the clinical effectiveness of two distinct newborn sequencing methods: one that targets well-established, medically actionable conditions (the actionable disease-centric method) versus another that takes an unbiased approach to evaluating all known genes associated with diseases (Balciuniene et al., 2023). The reportable WGS findings were associated with incomplete or age-dependent penetrance and variable expressivity, which is typical for a seemingly healthy population (Zschocke et al., 2023). Stratification of the genotypes by presumed penetrance revealed that almost half of the GS findings 46.8% were associated with high-penetrance conditions, in a total of 3.9% of the cohort (Balciuniene et al., 2023). Due to the diverse and clinically significant findings from WGS, the gene panels would need to cover many more genes, potentially even entire exons, to achieve the same clinical sensitivity as WGS.

This paves a path to the use of whole genome sequencing that can provide comprehensive answers to the ailing baby. urWGS is a variant of WGS that returns results back in a short turnaround time, reducing the time for diagnosis and aiding effective medical management of the baby.

Case study

In some cases, infants who were deteriorating rapidly were diagnosed and treated within days, with scientific evidence and helping clinicians to manage the child's health and have better prognosis. urWGS in conjunction with biochemical screening performed at Revvity Omics' laboratory in the United States, reported elevated levels of propionylcarnitine (C3) on the biochemical screening and pathogenic variant in *PDHA1* gene in a 3-day old male presented to his physician with hypotonia, significant birth defects, and metabolic acidosis in just 53 hours.[11]

The fast turn-around time allowed for an early detection and diagnosis in this child, which provided the healthcare providers with the ability to start with early intervention strategies to give this child the best possibility of an improved outcome. This chance would not have been possible without the lab's ultrarapid turnaround time and comprehensive genetic analysis.

This story underscores the potential of urWGS to not only save lives but to also offer hope to families during their most challenging moments.

The role of clinical labs: precision, and TAT

For clinical laboratories, the mandate is clear: deliver reliable, and comprehensive genetic information. Implementing urWGS workflows, integrating robust variant interpretation pipelines, and maintaining close collaboration with clinicians can dramatically improve neonatal outcomes.

By focusing on reduced turnaround times and actionable findings, labs play a critical role in not just shortening the diagnostic odyssey—but often ending it.

NGS is no longer a futuristic tool—it is today's necessity in the NICU. Early identification of genetic disorders through urWGS can change the trajectory of a newborn's life, enabling personalized care when it matters most. Newborn sequencing is expected to reduce the number of babies admitted to the NICU in the future, as national and state newborn screening programs will aim to identify infants with early-onset genetic diseases that might currently be missed by traditional biochemical and targeted molecular screenings. As we continue to push the boundaries of genomic medicine, clinical labs are at the heart of this transformation—ensuring that every newborn gets the chance at a healthier start.

Revvity Omics' comprehensive ultrarapid Whole Genome Sequencing (urWGS) offers a range of features, including mitochondrial genome sequencing, biochemical testing, cCMV analysis, SNV and CNV detection, and more.

With a turnaround time of 5-8 days and flexible sample types, included dried blood spots, our service is the most convenient and efficient option.

Revvity Omics confidently utilizes state-of-the-art genomic technologies to conduct advanced screening and diagnostic protocols. Our testing programs for newborns are designed for early detection and rapid intervention, giving you the confidence to make informed decisions.

At Revvity, we remain committed to powering innovation from discovery to cure. Our purpose is to expand the boundaries of human potential through science, and we intend to do this through research and development, by partnering with our customers to improve people's lives everywhere.

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Technology-Enabled Lactation Support for Neonatal Intensive Care and Beyond

Jaylee Hilliard, MSN, RN, NEA-BC, CPXP, Monique Landor, MSN, RNC-NIC, CLC, and Bailey Parette, MBA, BSN, RN, CLC

Breastfeeding is highly beneficial for infants within the NICU and other intensive care settings, promoting growth, enhancing neurodevelopmental outcomes, and reducing the risk of complications such as necrotizing enterocolitis (NEC). Yet, NICU parents encounter significant obstacles in establishing a successful breastfeeding journey, including prolonged separation from their infants, inconsistent breastfeeding support, birth complications, and NICU-related stress. These factors, coupled with breast-pump dependency, can contribute to difficulties in reaching the same target milk volumes as mothers of healthy, term breastfeeding infants.[1]

Technology can enhance family engagement and provide consistent, personalized lactation support to parents of infants in intensive care settings, empowering them to surpass these obstacles. By tracking lactation progress, giving access to virtual breastfeeding support and educational resources, and providing opportunities for connection, healthcare providers can offer well-timed guidance that supports mothers throughout their breastfeeding experience.

This article explores key strategies for technology-enabled lactation support and highlights how AngelEye Health's family engagement platform can help lactation professionals implement these strategies.

Figure 1. The six key elements in the lactation journey supported by AngelEye's platform.

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Strategies for Technology-Enabled Lactation Support

Technology can improve access to lactation support for parents with infants in NICUs and other intensive care settings. Live-stream video can increase milk production by connecting parents virtually with their infants. Mobile apps that track breastfeeding sessions and pumping trends help parents monitor progress. Tele-lactation services connect families with lactation consultants for remote consultations, personalized pumping plans, and ongoing support.[2]

Providing Meaningful Insights

External validation was key in parents' perception of their breastfeeding journeys.[3] Additionally, pumping logs have been associated with increased ratios of breast milk feedings, with exclusive breast milk feedings reducing the number of days Very Low Birthweight (VLBW) infants spent NPO (nothing by mouth).[4] By utilizing electronic pumping diaries, technology can create added value for parents. Viewing reports or session logs can act as a form of external validation for these parents and a starting point for more in-depth conversations with lactation professionals.[5]

Access Beyond the Bedside

Technology supports and delivers education to families even when they are not physically present in the ICU. Virtual family engagement technology enables parents to remain an integral part of the healthcare team, allowing them to receive updates on their baby's progress and communicate more frequently with healthcare providers. These types of technological tools are an effective way to educate parents and increase parental self-efficacy.[6] Additionally, facilitating remote lactation support has been demonstrated as an effective intervention for increasing breastfeeding in the NICU.[7]

Equity for All Families

For families whose primary language is not English, the inability to directly communicate with healthcare providers in their preferred language can create significant obstacles to receiving adequate updates and lead to heightened parental stress.[8] These communication barriers can be particularly challenging for parents trying to breastfeed or pump for their baby. However, family engagement technology can be crucial in bridging this communication gap and providing much-needed support to these families.

Applications with translation capabilities can facilitate real-time communication between parents and healthcare

providers, allowing for more effective and culturally sensitive conversations about breastfeeding. Additionally, online resources and educational materials can be translated into multiple languages, making them accessible to a broader range of families. By leveraging these technological tools, healthcare providers can better support non-English-speaking families in their breastfeeding journeys, fostering a sense of inclusivity and reducing parental stress, ultimately improving overall health outcomes.

Envisioning Technology-Enabled Lactation Support with AngelEye Health

Developed with insights from clinicians and lactation professionals, AngelEye's Family Engagement Platform offers several technology-driven solutions that can be leveraged to support lactation and improve the breastfeeding experience for families with infants in the NICU or other acute and intensive care settings.

Pump Session Tracking

The integration of pump session tracking into AngelEye's platform streamlines the data collection process for both parents and healthcare providers, enhancing lactation support by:

- **Camera Connection:** Viewing their child's live-stream camera during pump sessions can increase parental bonding and boost milk production.[9]
- **Consistency with Reminders:** Pumping reminders allow parents to set a "pumping goal" for the number of pump sessions in 24 hours and receive automated reminders to help them meet their goals and maintain consistency.
- **Session Logs and Reporting:** Parents and staff can easily track milk supply trends and inventory levels to better support and encourage mothers' own milk production with informed guidance.

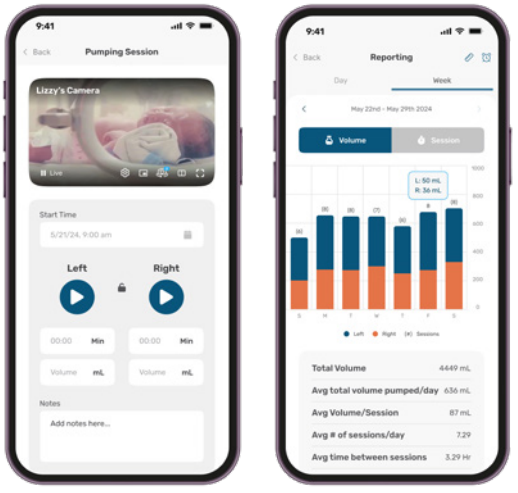

Figure 2. Parent's view of MilkTracker, tracking pump sessions and monitoring milk output.

Multi-modal Pathway for Education

Using varied education methods and modalities for delivery has been demonstrated as an effective way to improve education outcomes for NICU families.[10] Within the AngelEye platform, several features exist to help disseminate the correct information to parents at the right time:

- **Multi-media messaging:** Allows lactation professionals to share unit-curated resources such as flyers for lactation clinics and photo or video messages.
- **Education Content:** Empower and inform families with customized education supporting breast milk production and breastfeeding, featuring video content and articles that remain accessible to parents beyond their child's discharge date.
- **Built for Equity:** With translation into 70+ languages and content aimed at a 5th-grade reading level, AngelEye's platform seeks to remove barriers to health literacy, making breastfeeding support accessible to all families.

Personalized Support

Emotional support from the community and external validation play a key role in parents' perception of their breastfeeding journeys.[4] In challenging intensive care environments, lactation professionals can utilize the following features to assist in meeting these needs:

- **Announcements for Support Groups:** Announcements allow lactation professionals to share reminders about in-person support groups with parents by pinning information to the parents' home screen within the AngelEye app.
- **In-app Conversations:** Combined with AngelEye's translation capabilities, two-way messaging allows for lactation consultation to extend beyond the bedside and past language barriers so all parents have dedicated support from a lactation professional.
- **Actionable Surveys:** Automated, adaptable assessments inform real-time, personalized care adjustments and clinical feedback to enhance outcomes and satisfaction.

Milk Management and Inventory

AngelEye's MilkTracker Feeding Management solution prioritizes safety at every step of the feeding process and offers families informed ownership in milk management. Several features can be utilized to support the safety and efficacy of milk management:

- **Enhanced Safety:** Recipe calculation, barcode scanning, and product-tracking offer safer patient feeding administration[11] and are all features available in the MilkTracker solution. With parental stress increased in the unfamiliar NICU or other intensive care environments, enhanced safety can help palliate parental anxiety.
- **Milk Inventory Alerts:** By providing parents with updates on the mother's milk inventory at the hospital, technology can help parents balance the transport of breastmilk to the NICU with their competing external responsibilities to promote parental well-being.[12]
- **Self-Serve Printing for Parents:** With self-service label printing, parents can independently print pump/parent labels for their baby without assistance from clinicians or staff, removing one common pain point for parents transporting breast milk to the ICU.

Envisioning the Future: How AI and Technology Could Transform Lactation Support Across Care Settings

Advancements in AI, sensors, cameras, algorithms, and predictive analytics offer transformative potential for lactation support across the NICU, pediatric units, and during the transition to home. These technologies could personalize care by analyzing real-time data on milk production, pumping frequency, and infant feeding patterns, enabling tailored recommendations for optimized milk production. Predictive analytics could proactively identify lactation issues, prompting timely interventions like remote consultations or schedule adjustments, reducing risks, and improving infant and family outcomes.

AI-enhanced tools could further improve lactation support with virtual consultations, real-time monitoring, and data integration. By analyzing live-streamed video, AI could detect issues such as improper latching or pump difficulties, triggering immediate feedback from lactation professionals. Additionally, AI-powered systems could streamline milk tracking and inventory management, ensuring safety and efficiency. Real-time translation and personalized educational content would also help bridge language barriers, making lactation support more inclusive. As AI and technology evolve, these innovations will provide continuous, data-driven care, ultimately enhancing breastfeeding outcomes and strengthening the parent-child bond across all care settings.

Conclusion

AngelEye Health's suite of technology solutions—MilkTracker, NICU2Home, CameraSystem, and pump session tracking—play a pivotal role in enhancing lactation support for families in the NICU, PICU, and other intensive care units. By improving parent engagement, fostering emotional connections, and ensuring real-time monitoring of breastfeeding efforts, these tools significantly contribute to better breastfeeding outcomes, higher parental satisfaction, and improved infant outcomes across various care settings. As technology evolves, AngelEye's solutions will remain at the forefront of improving lactation support, ensuring families in NICUs, pediatric units, and critical care areas receive the best possible care throughout their journey.

To explore how AngelEye Health's Family Engagement Platform can support lactation efforts in your hospital, visit angeleyehealth.com.

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Mortality Reduction: A 15-Year Case for Widespread Adoption of an Exclusive Human Milk Diet

Sandra Sullivan, MD, IBCLC and Kate Tauber, MD

Introduction

When caring for fragile infants in the neonatal intensive care unit (NICU), the joy and relief experienced by both the clinical team and family when an infant straddling the line between life and death is successfully discharged home is unmatched. As neonatologists working in NICUs for 23 years and 16 years, respectively, we have witnessed many innovations that have markedly increased the likelihood that very low birthweight (VLBW) infants will make it through those critical first weeks, surviving to discharge with every hope for long, healthy lives.

One of these innovations is the use of an exclusive human milk diet (EHMD) among infants born weighing ≤ 1,500 g. Despite seeing in real time how an EHMD changes VLBW infants' trajectories for the better, NICUs that lack the clinical staff to directly champion this intervention may fail to implement it or let it drop off the radar. In 2024, 50% of Level III and IV NICUs in the U.S. used human milk-based fortifiers for the tiniest preemies in their care. Why not all high-level NICUs? For those of us who have seen what an EHMD can do, the resistance to adopting it is a frustration that we find difficult to put into words. In fact, witnessing the missed opportunities is so discouraging that we have made it part of our professional life's work to help get an EHMD to the infants who need it most.

Let's take a look at some highlights from the last 15 years' worth of mortality evidence that has made us such strong believers in an EHMD.

Evidence of Mortality Benefits of an EHMD

The real potential of an EHMD came to our, and many others', attention in 2010 when Sullivan et al randomized 207 infants born weighing 500 to 1,250 g and fed mother's own milk (MOM) to one of three feeding groups. The first received human milk-based fortifier (HMF) at 100 mL/kg/d plus donor milk (DM), if needed. The second received HMF at 40 mL/kg/d plus DM if needed. The third received cow milk-based fortifier (CMF) at 100 mL/kg/d and preterm formula (PTF) if no MOM was available. The infants in the two EHMD groups had significantly lower rates of necrotizing enterocolitis (NEC) (P = 0.02) and surgical NEC (P = 0.007).[1]

This study was a watershed moment because NEC is one of the most serious complications that affects VLBW infants and is a leading cause of death, especially amongst those who are born smallest. The findings spurred additional research, both to confirm these findings and help uncover what additional benefits an EHMD might offer. It was also the major instigator behind a move to provide DM over formula when MOM was not available. If the cost savings associated with an EHMD were known then as they are today, we believe that an EHMD would have been adopted universally.

These initial hints at a mortality benefit with an EHMD were fully borne out for the first time in 2014, with the publication of a retrospective analysis of 381 infants born weighing ≤ 1500 g. This time, outcomes were examined based on one of three feeding protocols: PTF given exclusively or MOM fortified with CMF and PTF; MOM/DM plus CMF; or MOM/DM plus HMF. This time the EHMD group had a lower risk of NEC vs. the PTF group (OR = 0.060) as well as a lower risk of NEC *and* gastrointestinal bleeding vs. those who received MOM/DM plus CMF (OR = 0.070).[2] While not a key endpoint of the trial, a mortality benefit was observed for the first time with an EHMD in this trial. Compared with PTF, an EHMD was correlated with a lower odds of mortality (OR = 0.040; CI = 0.001-0.456; P = .021), as was MOM/DM plus CMF vs. PTF (OR = 0.158; CI = 0.024-0.854; P = .036). Note that patients were put on an EHMD *only* if they were at increased risk for NEC, so they were already at a disadvantage.[2]

A confirmation of the mortality benefits with an EHMD was provided by Abrams et al., also in 2014. He reanalyzed the data from Sullivan 2010, adding to it results of a small, randomized trial by Cristofalo et al, which demonstrated a trend toward reduced NEC (P = 0.08) and significant reduction in surgical NEC (P = 0.04) with an EHMD vs. PTF among 53 VLBW infants.[3] In the Abrams study, infants who received an EHMD (n = 167) were compared against those who received cow milk-based protein (n = 93). An EHMD was associated with significantly lower rates of mortality (P = 0.004) and NEC (P = 0.002). Also, for every 10% increase in the volume of milk containing cow milk-based protein, the risk of sepsis increased by 17.9% (P < 0.001). This study not only confirmed the findings of Huston and Sullivan, but also demonstrated

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that *any use of cow milk-based protein* could put vulnerable infants at unnecessary risk.[4] What worked best for VLBW infants was an EHMD.

Reconfirmation in a larger sample occurred in 2016, with a multicenter retrospective cohort study of 1,587 infants born weighing ≤ 1250 g. This time, an EHMD was associated with a reduced risk of mortality (13.6% vs. 17.2%), as well as NEC (6.9% vs. 16.7%), late-onset sepsis (19.0% vs. 30.3%), retinopathy of prematurity (5.2% vs. 9%), and bronchopulmonary dysplasia (47.7% vs. 56.3%), compared with MOM plus PFT/CMF ($P \leq 0.04$ for all comparisons).[5]

In 2021, Bushati et al compared outcomes of 15 extremely low birth weight (ELBW) infants who received an EHMD as part of a quality improvement measure with a historical cohort of 49 ELBW infants who received CMF. They found improved feeding tolerance with an EHMD. In addition, there were no deaths among the infants fed an EHMD, while the mortality rate was 8.2% in the historical cohort.[6]

The inevitable systematic review and meta-analysis on the benefits of an EHMD was published in 2024. It included four studies, comprising 681 infants born weighing ≤ 1,500 g. Infants fed with MOM/DM were compared based on whether their diets were fortified with HMF or CMF. Mortality risk was significantly reduced (RR = 0.50, 95% CI = 0.26–0.94; p = 0.03; $I^2 = 0\%$) with an EHMD.[7] This confirms the mortality benefit of an EHMD in VLBW infants, using the highest level of evidence available.

Cost Effectiveness Plus Mortality Benefits Observed

As the studies showing benefit piled up, questions about the cost-benefit of an EHMD were increasingly addressed. Hampson et al conducted an economic analysis exploring the costs of using an EHMD in VLBW infants vs. usual practice (which included cow milk-based nutrition), using the Abrams 2014 and Hair 2016 datasets. In addition to showing cost savings of $16,309 per infant, implementation of an EHMD was shown to result in 36 fewer deaths per 1,000 patients vs. usual care.[8]

In 2019, Scholz and Grenier conducted a cost-effectiveness study of implementing an EHMD among VLBW infants in Germany. They estimated that an EHMD was cost-effective compared with nutritional protocols that included cow milk-based protein, with an incremental cost-effectiveness ratio of €28,325 (approximately $31,895) per life-year-gained. Perhaps more compellingly, their model revealed that 290 deaths would be prevented annually with the adoption of an EHMD.[9]

How did we get here?

Given the wealth of evidence over the last 15 years that an EHMD is the best possible nutrition for select VLBW infants, it begs the question, why are some units still resisting the implementation of this important change? There is no identified risk, only potential benefit, to implementing an EHMD. While the initial costs are higher, multiple studies have demonstrated that, in appropriate patients, cost savings are significant, due to reduced complications, particularly surgical NEC and hospital length of stay.[2,8-13]

So, what is the source of the resistance? First and foremost is the financial reality of reimbursement in the U.S. The cost of human milk-based fortifier is usually covered through the NICU's budget, but the cost savings is typically felt by private or public insurers. Even when insurers cover the cost of human milk-based fortifier, it is usually included as part of a calculated lump sum for NICUs to dispense at their discretion. When there is a pressing need for a new ventilator or more nursing hours, it can be a tough call to earmark that money for HMF, especially when many NICUs in the U.S. receive cow milk-based nutrition at deep discounts or even free of charge from formula companies.

A second issue is the culture of the NICU. This is an environment where doing more with less is the norm, unlike departments such as surgery or radiology, where having the most advanced and updated tools and equipment are well-recognized to be essential to both improving patient outcomes and attracting top talent. NICU specialists also have an understandably strong sense of loyalty to formula companies, as they support a large portion of the research and education that goes into skills training and career development. Formula companies also directly support NICUs by providing nutrition and related tools free of charge and have demonstrated their dedication to infant health by spearheading research into infant nutrition. It is undeniably true that formula companies provide excellent nutritional support for NICU patients. It is also true, however, that a subset of those infants will fare better on an EHMD.

Where do we go from here?

It is time to recognize the important benefits of an EHMD and to ensure that our most vulnerable patients are given every appropriate intervention to achieve their utmost potential in the NICU and beyond. While cow milk-based nutrition is suitable for larger premature infants, these products do not offer the outcomes that an EHMD does for VLBW infants. The improved outcomes match those of costly medical interventions that we do not think twice about providing, such as high frequency ventilation or inhaled nitric oxide. Most hospital NICUs will provide an EHMD to appropriate VLBW infants when there is a champion who advocates for it. You can be that champion, or you can speak to faculty in your NICU about taking on that role. Make sure your NICU is aware of the benefits and 15 years of mortality evidence of an EHMD and stand up for the fragile and vulnerable patients who need this life-saving intervention. They need you to advocate for their future.

Conclusions

Given this wealth of mortality evidence, it mystifies and frustrates us that an EHMD is not standard of care among appropriate VLBW infants in hospital NICUs across the U.S. and globally. The evidence is strong enough to merit a widespread practice change. Why are we letting infants suffer when we have an intervention that might save them? We know better, so now it is time to do our best for our most vulnerable patients and implement an EHMD when appropriate.

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The Association of Early Antibiotic Exposure With Subsequent Development of Late-Onset Sepsis in Preterm Infants: A Systematic Review and Meta-Analysis Studies

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Abstract

Background

Early antibiotic exposure in preterm infants may disrupt gut microbiome development, affecting health. However, its link to late-onset sepsis (LOS) remains unclear. This meta-analysis aims to clarify the association while addressing confounding bias.

Methods

This systematic review and meta-analysis, conducted per PRISMA guidelines, utilized PubMed, Scopus, Google Scholar, and Web of Science for comprehensive literature retrieval. Studies comparing preterm infants with sterile blood cultures who received early antibiotics (short or prolonged) to those without, using LOS as the primary outcome, were included. Comparisons between short- and prolonged-course antibiotics were also considered. Only studies with adjusted analyses for confounders were considered. Adjusted odds ratios (aOR) were meta-analyzed, and the prediction interval (PI) was calculated using R software.

Results

Ten studies met the eligibility criteria, comprising a total sample size of 55,089 preterm infants. Among these, nine studies included 33,549 preterm infants and compared prolonged antibiotic exposure to short exposure. Prolonged exposure was not significantly associated with LOS (pooled aOR = 1.2, 95% CI 0.99–1.46, P = 0.066, PI = 0.66 to 2.19, I^2 = 67%). Limiting the analysis to five studies with sample sizes over 1,000 reduced heterogeneity (I^2 = 30%) and provided a more precise confidence interval (pooled aOR = 1.03, 95% CI 0.91–1.15). Four studies, involving 41,938 preterm infants, examined preterm infants exposed to prolonged antibiotics versus those not exposed and found no significant association (aOR = 0.91, 95% CI 0.82–1.02, P = 0.1, PI = 0.72 to 1.16, I^2 = 0). All four studies had sample sizes exceeding 1,000. Additionally, these studies compared preterm infants with short antibiotic exposure to non-exposure, revealing a slightly lower risk of LOS (aOR = 0.87, 95% CI 0.77–0.98, P = 0.024, I^2 = 0) and a PI of 0.76 to 1.14.

Conclusions

Our findings indicate that prolonged early antibiotic exposure in preterm infants with sterile cultures does not significantly increase the risk of LOS compared to no antibiotic exposure. Interestingly, a shorter duration of antibiotic exposure might be associated with a slightly lower risk of LOS.

Background

Neonatal sepsis is one of the primary causes of mortality at the neonatal intensive care unit (NICU).[1] In addition, it is the leading driver of antibiotic prescriptions in NICU.[2] It typically presents modest and nonspecific signs overlapping with many clinical conditions, for instance prematurity-related events. Therefore, clinicians often extend empirical antibiotic therapy even in the absence of positive blood cultures or clinical signs.[3-5] Antibiotics are initially administered to prevent delayed sepsis diagnosis, while their prolonged use aims to reduce the risk of relapse or undertreatment. A worldwide investigation involving preterm infants in 84 NICUs across 29 countries showed that 92% of infants received antibiotics.[4]

This unnecessary antibiotic treatment may result in several neonatal adverse outcomes, especially in early life. Previous studies indicate that antibiotic exposure in preterm infants with sterile cultures increases the risk of experiencing adverse events such as necrotizing enterocolitis (NEC),[6] late-onset sepsis (LOS),[7-9] and mortality.[8,10] However, the evidence concerning LOS remains inconclusive. Some studies suggest an increased risk of LOS,[7-9] however, these studies have smaller sample sizes, which could potentially lead to an overestimation of the odds ratio due to the small sample size. Others find no significant association.[3,11-13] Moreover, a recent case-control study showed that antibiotic exposure before the onset of LOS was associated with decreased odds of gram-positive LOS.[14] Similarly, a prior study utilizing preterm pigs as a model demonstrated that oral administration of broad-spectrum antibiotics to preterm infants delayed gut bacterial colonization, improved blood neutrophil maturation, and provided protection against bacteremia.[15]

In this study, our objective was to identify, critically assess, and synthesize evidence from studies that investigate the association

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of early antibiotic short or prolonged exposure in preterm infants with negative cultures with the subsequent risk of LOS. To mitigate the potential for confounding, we selectively included studies that adjusted for confounders. Furthermore, we stratified the results based on sample size to minimize the overestimated risk in studies with a small sample size.

Methods

Search strategy

We conducted a thorough literature search from inception to June 1, 2024, using PubMed, Scopus, Google Scholar, and Web of Science databases. The detailed search strategy is provided in Table S1. Additionally, the reference lists of all included studies were systematically screened to identify any additional eligible articles. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Table S2 includes the PRISMA checklist outlining the items covered in this systematic review's reporting.

Eligibility criteria

Inclusion criteria (PICO Format)

The inclusion criteria were structured using the PICO format as follows:

- **Population:** Preterm infants with sterile blood cultures.
- **Intervention:** Exposure to antibiotics for a specified duration, either a prolonged or short period of exposure.
- **Comparison:** Preterm infants who received antibiotic therapy (prolonged or short course) versus those who did not. Additionally, studies comparing short-course vs. prolonged antibiotic therapy were included.
- **Outcome:** blood culture-confirmed LOS cases.
- **Additional Criteria:** Studies included adjusted analyses to account for potential confounding factors.

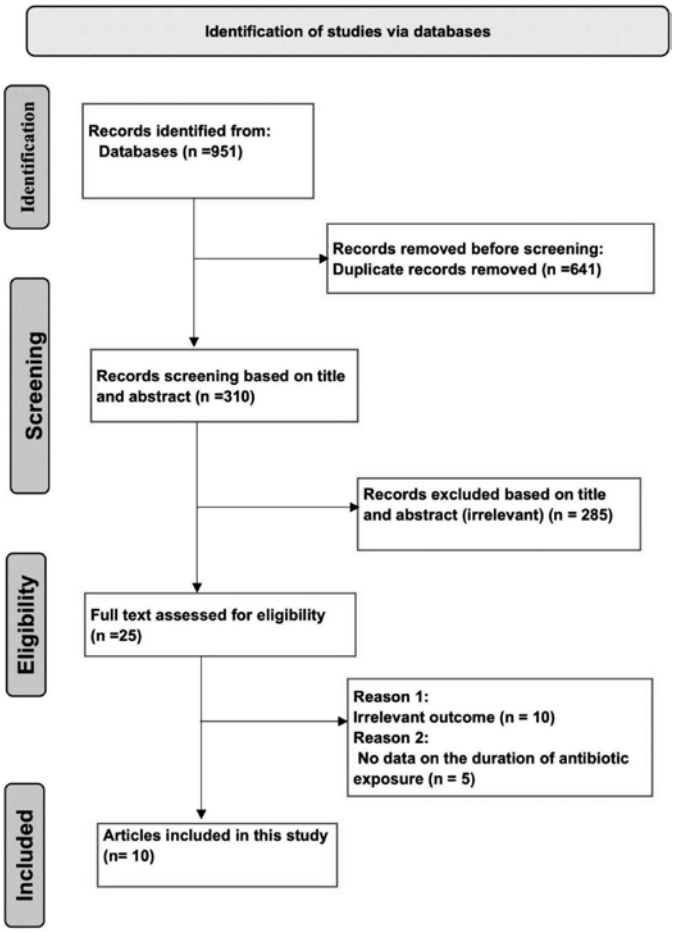

Figure 1. PRISMA flow diagram of study selection process.

Exclusion criteria

Preterm infants who developed culture-proven sepsis, case reports, letters, reviews, not peer-reviewed publications and editorials.

Study selection

We initiated the search by entering relevant keywords into the selected databases, creating individual libraries for each database. Duplicates were removed using Zotero 6.0. We then proceeded with the step-by-step selection of eligible articles. Initially, we excluded articles based on their titles, eliminating those deemed completely irrelevant. If there was any doubt, we retained the article for further evaluation in subsequent steps. The remaining articles were assessed for eligibility based on their abstracts and full texts. Additionally, we reviewed the reference lists of the eligible articles to identify any potential additional eligible studies. Six reviewers independently selected the relevant articles based on the previously mentioned inclusion and exclusion criteria.

Definitions

LOS was defined as the isolation of pathogenic bacteria from blood and/or cerebrospinal fluid cultures, or fungi from blood cultures, occurring more than 72 h after birth.[16] The definition of early empirical antibiotic administration varied across studies; however, for the purposes of this study, it was considered as antibiotics administered within the first week after birth encompassing both short-course and prolonged exposure. There is no consensus definition for prolonged and short antibiotic exposure antibiotics, so we report the specific definitions used by each study's authors.

Data extraction

Two reviewers independently extracted the necessary data from each included study. Two additional reviewers then cross-checked the extracted data to ensure accuracy and consistency.

Risk of bias assessment

To assess the risk of bias of the included studies, we employed the Newcastle Ottawa Scale (NOS).[17] This scale evaluates studies in three key areas: selection, comparability, and outcome. The checklist items are presented in Table S3. The NOS scoring system has a maximum of 9 points, with studies receiving a maximum of one point for each criterion within the selection and outcome domains. In the comparability domain, a maximum of two points can be awarded. Each eligible article was independently assessed by three reviewers, and any scoring discrepancies were resolved through discussion and consensus among all authors.

Data synthesis

We reported the results as pooled adjusted odds ratios (aOR) with 95% confidence intervals (CI). We conducted a subgroup analysis of studies with over 1000 participants to mitigate the overestimation of ORs.[18] and minimize the risk of publication bias in smaller studies. The pooled estimates were calculated under the random-effects model, which accounts for variability both within and between studies. Heterogeneity between the studies was assessed using I-squared. In addition, we reported

Table 1 Characteristics of the included studies

Last name of the first author (publication year)	Total number of preterm infants	# Centers	Gestational age or weight	Cutoff of prolonged antibiotic exposure (Days)	Adjustment methods	Adjusted factors	NOS (out of 9)
Kuppala (2011) [7]	305	Multicenter	< 32 weeks	≥ 5	Multivariable logistic regression	**Maternal Factors** PROM **Infant Factors** Birth weight, GA, Race **Clinical Factors** High-frequency ventilation Received breast milk and Apgar score at 5 min	**8**
Cotten (2009) [3]	5693	Multicenter	ELBW	≥ 5	Multivariable logistic regression	**Maternal Factors** prenatal steroid use, prenatal antibiotic use, hypertension, PROM, hemorrhage **Infant Factors** race, gender, GA, SMA, multiple births **Clinical Factors** 5-minute Apgar score, center, mechanical ventilation, early initiation of enteral feeds	**9**
Ting (2019) [13]	14,207	Multicenter	VLBW	≥ 4	Multivariable logistic regression	**Maternal factors** PROM **Infant factors** GA, multiple births **Clinical factors** SNAP-II scores, extensive CPR, surfactant use, mechanical ventilation, inotropes and pneumothorax treated with chest tube	**9**
Greenberg (2019) [20]	5730	Multicenter	< 28 weeks	≥ 5	Multivariable logistic regression	**Maternal factors** Black race, Multiple birth, PROM > 24 h, Receipt of antenatal steroids, Perinatal antibiotic therapy, Hypertension, Antepartum hemorrhage, Cesarean section **Infant factors** GA, SGA, Sex **Clinical factors** 5-min Apgar score < 5, Birth year, Center, Mechanical ventilation	**9**
Dierikx (2022) [12]	1259	Multicenter	< 30 weeks	> 3	Multivariable logistic regression	**Maternal factors** Mode of delivery (vaginal, c-section) **Infant factors** Gender, Birth weight percentile, GA **Clinical factors** Center, Days of parenteral feeding, Invasive ventilation support, Inotropic medication use type of enteral feeding and Apgar score 5 min	**9**
Fajardoa (2018) [9]	620	Single center	VLBW	> 5	Multivariable logistic regression	**Maternal factors** Maternal hypertension, Prenatal steroid treatment and Intrapartum antibiotic treatment **Infant factors** SGA, Gender and Multiple births **Clinical factors** SNAP II and Clinical chorioamnionitis	**8**

the prediction interval (PI), which indicates the range within which the true effect size is expected to fall for 95% of all populations.[18] Publication bias was assessed using a funnel plot and Egger's regression test. All statistical analyses were performed using the R programming language (version 4.0.2). Specifically, the meta-analysis was conducted utilizing the 'meta' and 'metafor' packages.

Results

Characteristics of eligible articles

This systematic review included ten original research studies with a total of 55,089 preterm infants[3,7-9,11-13,19-21] as shown in Fig. 1. The characteristics of eligible articles are displayed in Table 1. In four studies, the sample sizes were relatively small, with less than 1000 infants.[7-9,19] Conversely, six studies had larger sample sizes, with more than 1000 infants.[3,11-13,20,21] Among these, two large studies included over 10,000 infants.[13,21] Eight studies were conducted across multiple centers.[3,7,11-13,19-21] In contrast, two studies were conducted at a single center.[8,9] All studies followed a retrospective observational study design, except for those that utilized a prospective observational study design.[8,12] Antibiotics were started early in all the studies included. The definition of prolonged exposure to antibiotics varied across the ten studies: lasting for ≥ 5 days in five studies;[3,7,9,20,21] for ≥ 4 days in four

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NOXIVENT® Indication and Important Safety Information

Indication

NOXIVENT® is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

Contraindications

Noxivent is contraindicated in neonates dependent on right-to-left shunting of blood.

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Airway Injury from Nitrogen Dioxide: Monitor nitrogen dioxide (NO_2) levels. Nitrogen dioxide may cause airway inflammation and damage to lung tissue.

Heart Failure: In patients with pre-existing left ventricular dysfunction, Noxivent may increase pulmonary capillary wedge pressure leading to pulmonary edema.

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The most common adverse reaction of NOXIVENT is hypotension.

Drug Interactions

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Administration

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Table 1 (continued)

Last name of the first author (publication year)	Total number of preterm infants	# Centers	Gestational age or weight	Cutoff of prolonged antibiotic exposure (Days)	Adjustment methods	Adjusted factors	NOS (out of 9)
Yu (2023) [21]	21,540	Multicenter	< 34 weeks	≥ 5	Multivariable logistic regression	**Maternal Factors** Maternal hypertension, Maternal diabetes, Maternal steroid use, Cesarean section **Infant Factors** GA, Male, SGA, 5-minute Apgar score ≤ 7 **Clinical Factors:** Mechanical ventilation, Vasopressor treatment, Breastmilk feeding, Age of enteral feed initiation	**9**
Vatne (2023) [11]	4932	Multicenter	< 32 weeks.	≥ 4	Multivariable logistic regression	**Maternal Factors** Mode of delivery, Antenatal steroids **Infant Factors** GA, Sex, Multiple births, Birth weight, Year of birth, Birth region **Clinical Factors** Antibiotics, Days of mechanical ventilation, CRIB2, Apgar score, Intraventricular hemorrhage	**9**
Shah(2013) [8]	216	Single center	< 28 weeks	≥ 4	Multivariable logistic regression and similar baseline characteristics	**Maternal factors** PIH, APH, Mode of delivery, Maternal antibiotics, Antenatal glucocorticoids **Infant factors** GA, Birth weight, IUGR, gender **Clinical factors** Chorioamnionitis, PROM, CRIB score, Apgar score	**7**
Alsafadi (2018) [19]	587	multicenter	< 34 weeks	≥ 4	Multivariable logistic regression	**Birth weight**, **gestational age**, **gender**, **mode of delivery**, **PROM**, **pregnancy-induced hypertension**, **multiple births**, **asphyxia**, **sepsis laboratory tests**	**7**

NOS, **Newcastle Ottawa Scale; PROM**, **Premature Rupture of Membranes; GA**, **Gestational Age; CRIB**, **Clinical Risk Index for Babies; SGA**, **Small for Gestational Age; IUGR**, **Intrauterine Growth Restriction; PIH**, **Pregnancy-Induced Hypertension; APH**, **Antepartum Hemorrhage; Apgar**, **Appearance**, **Pulse**, **Grimace**, **Activity**, **Respiration; SNAP-II**, **Score for Neonatal Acute Physiology-II; SMA**, **Sall for Gestational Age**

studies;[8,11,13,19] and for > 3 days in one study.[12] All the studies employed multivariable logistic regression for the adjustment of the confounders. The overall risk of bias assessment in Table 1 was low, although some studies had a higher risk (lower scores, such as 7) due to small sample sizes and inadequate adjustment for confounders.[7,19]

Other characteristics include setting/country, study design, birth years of cohort, total numbers of participants, total number of preterm infants with either prolonged or short early exposure to antibiotics. Others without exposure to antibiotics (0 days), and Late-Onset Sepsis Cases by Duration of Exposure; all are included in table S4.

Risk of LOS in preterm infants exposed to prolonged antibiotics vs. Short exposure

Nine studies, involving a total of 33,549 preterm infants, investigated the risk of LOS associated with prolonged antibiotic exposure compared to short exposure (defined as > 5 days vs. <5 days in five studies and ≥ 4 days vs. <4 days in three studies). Prolonged antibiotic exposure was not significantly associated with an increased risk of LOS (pooled aOR = 1.2, 95% CI 0.99–1.46, $P = 0.066$), as illustrated in Fig. 2. The prediction interval was wide, ranging from 0.66 to 2.19. Additionally, substantial heterogeneity was observed among these studies ($I^2 = 67\%$). Publication bias testing using the funnel plot and Egger's regression analysis revealed no evidence of publication bias, with an Egger's test p value of 0.27, as shown in Fig. 3. Restricting the analysis to five studies with sample sizes exceeding 1000 resulted in decreased heterogeneity ($I^2 = 30\%$, total sample size = 31,821) and a non-significant association between prolonged exposure and LOS, with a narrower confidence interval and greater precision (pooled aOR = 1.03, 95% CI 0.91–1.15), as delineated in Fig. 2.

The subgroup analysis of studies with sample sizes less than 1000 showed a pooled aOR of 1.71 (95% CI 1.14 to 2.56), indicating a significant association between prolonged antibiotic exposure and LOS. This subgroup exhibited substantial heterogeneity, as evidenced by an I^2 value of 78%.

Risk of LOS in preterm infants exposed to prolonged antibiotics vs. non-exposed

Four studies, encompassing a total sample size of 41,938 preterm infants, reported a pooled aOR of 0.91 (95% CI 0.82–1.02, $p = 0.1$) for the association between prolonged antibiotic exposure and LOS. The PI of 0.72 to 1.16 further supports the lack of a statistically significant effect, as shown in Fig. 4. In all of these studies, sample sizes were over 1000, and the results were homogeneous, as evidenced by the I^2 of 0.

Risk of LOS in preterm infants with short antibiotic exposure vs. non-exposure

Four studies, encompassing a total sample size of 41,938 preterm

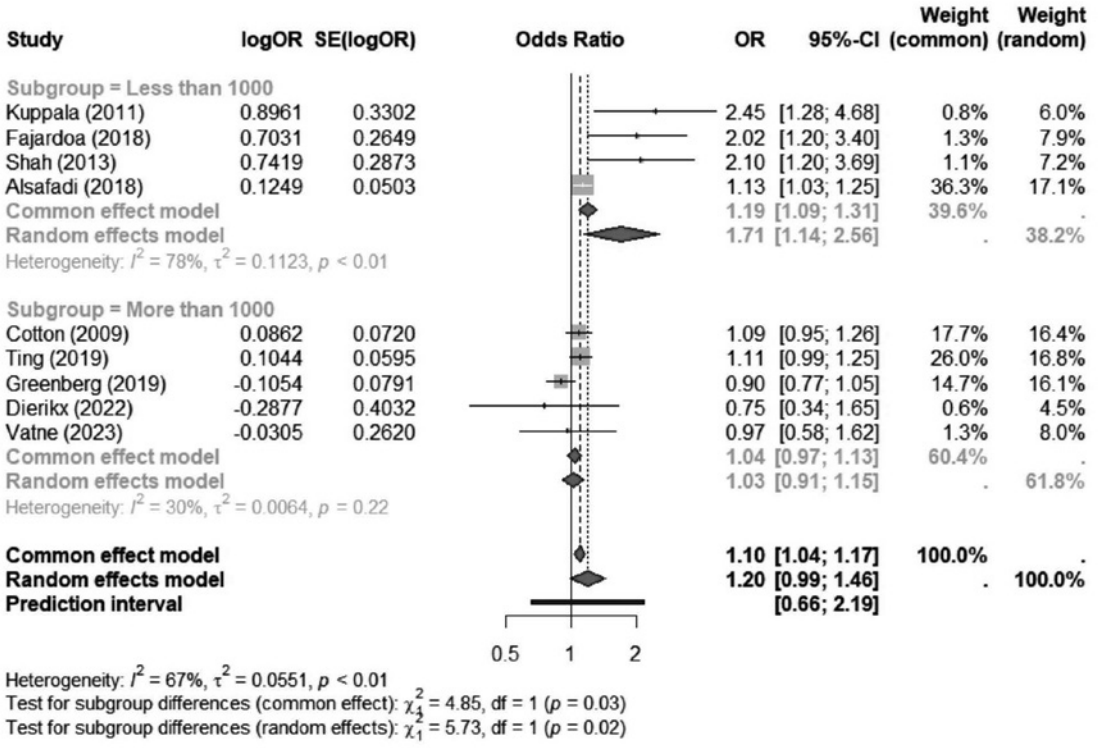

Figure 2. Meta-analysis of the risk of late-onset sepsis (LOS) in preterm infants exposed to prolonged versus short antibiotic courses, stratified by a sample size of 1000. This analysis includes nine studies with a combined total of 33,549 preterm infants.

infants, were meta-analyzed. All of these studies had sample sizes exceeding 1000, and the results were homogeneous, as evidenced by an I^2 of 0%. Overall, the risk of LOS was slightly lower for preterm babies who were exposed to antibiotics for a short duration compared to those who were not exposed (pooled aOR of 0.87, 95% CI 0.77–0.98, P = 0.024) with a slightly wide prediction interval of 0.67 to 1.14 as shown in Fig. 5.

Discussion

To our knowledge, this Meta-analysis is the first to investigate the risk of subsequent LOS in preterm infants with sterile cultures exposed to varying durations of antibiotics in early life. All the included studies adjust for neonatal, maternal and clinical confounders. Overall, our findings suggest that neither prolonged nor short antibiotic exposure is significantly associated with an increased risk of LOS in preterm infants. However, short antibiotic exposure may be linked to a slightly lower risk.

Antibiotic exposure in preterm infants can disrupt the natural balance of the gut microbiota, leading to a condition known as dysbiosis.[22] This disruption can significantly affect the development and function of the immune system, especially in preterm infants whose immune systems and microbiotas are still maturing.[22] The altered microbiota can impair both innate and adaptive immune responses, reducing the effectiveness of immune defenses against infections.[22] These changes may lead to increased susceptibility to infections and other immune-related conditions later in life.[22]

Two systematic reviews were undertaken to investigate the correlation between early antibiotic exposure and adverse neonatal outcomes. Esaiassen et al. focused on examining the association with necrotizing enterocolitis, invasive fungal infections, and mortality.[10] Nevertheless, this study was limited by the absence of quantitative data synthesis and the lack of information concerning confounder adjustment, highlighting significant constraints.[10] The other study addressed the risk of necrotizing enterocolitis in preterm infants who underwent extended empirical antibiotic treatment compared to those on a short antibiotic exposure[6] However, this meta-analysis predominantly utilized unadjusted data rather than adjusted effect sizes, prompting concerns regarding the accuracy of the conclusions drawn. Notably, no study specifically addressed the association between early antibiotic exposure and the subsequent risk of late-onset sepsis in premature infants with sterile cultures. In our investigation, we rely on studies that meticulously adjust for clinical neonatal and maternal confounders. Furthermore, we stratify the analysis based on sample size to mitigate the potential for inflated odds ratios in studies with smaller sample sizes[18]

In this study, prolonged exposure was not significantly associated with LOS (pooled aOR = 1.2, 95% CI 0.99–1.46, P = 0.066, PI = 0.66 to 2.19, I = 67%). Limiting the analysis to five studies with sample sizes over 1,000 reduced heterogeneity (I < 0xC6 > = 30%) and provided a more precise confidence interval (pooled aOR = 1.03, 95% CI 0.91–1.15). Notably, the smallest sample sizes in this group, from Kuppala et al.[7] with 305 preterm infants and Shah et al.[8] with 216 preterm infants, yielded the most significant results. Kuppala et al. reported an OR of 2.45 (95% CI 1.28 to 4.67), while Shah et al. reported an OR of 2.1 (95% CI 1.2 to 3.7). This may be attributed to the overestimated odds ratios in studies with small to moderate sample sizes.[18] Likewise, a prior meta-analysis that compared prolonged antibiotic exposure to short-term exposure concerning necrotizing enterocolitis revealed that both the odds ratio and heterogeneity

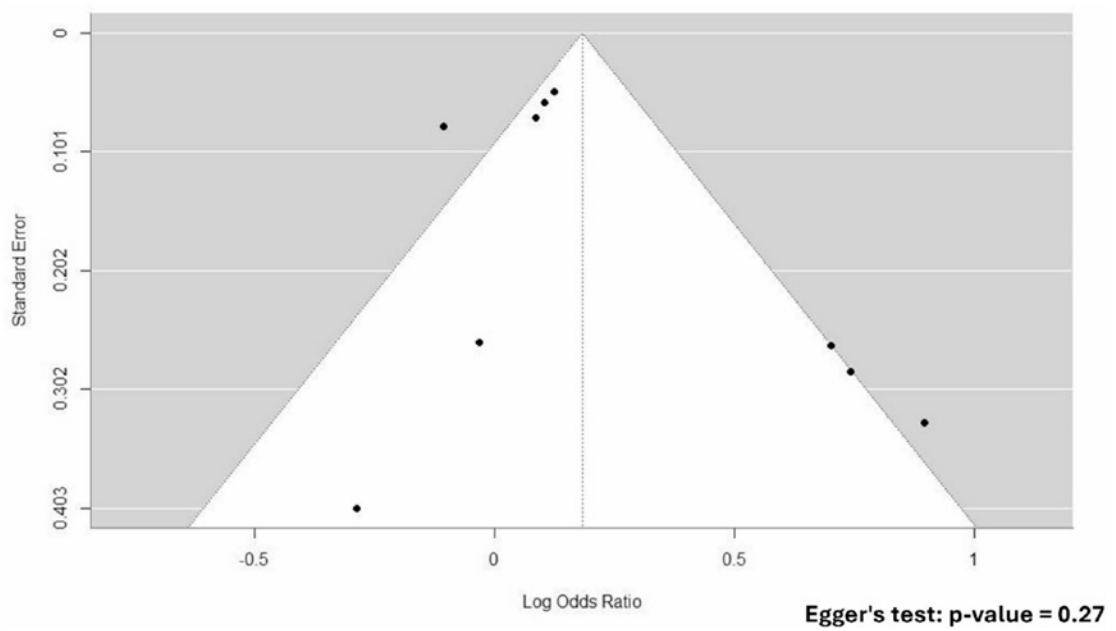

Figure 3. Funnel plot of the risk of late-onset sepsis (LOS) in preterm infants exposed to prolonged versus short antibiotic exposure. Egger's regression analysis showed no evidence of publication bias (Egger's test, p = 0.27).

were elevated in studies with smaller sample sizes. Specifically, the analysis indicated a substantial odds ratio of 2.66 (95% CI: 1.54–4.59) with significant heterogeneity (I^2 = 86%) for studies with sample sizes ranging from 200 to 500. Conversely, studies with sample sizes exceeding 1,000 exhibited a reduced odds ratio of 1.34 (95% CI: 1.16–1.55) and minimal heterogeneity (I^2 = 9%).

In comparison to preterm infants not exposed to antibiotics, those exposed for a short period exhibited a slightly reduced risk of LOS, with a pooled aOR of 0.87 (95% CI 0.77–0.98, P = 0.024). This protective effect could be associated with a milder impact on the gut microbiota during short-term exposure compared to prolonged use, and potentially prompt eradication of suboptimal infections at an early stage. This was supported by a case-control study that found antibiotic administration reduced the risk of LOS in preterm infants. Specifically, the study reported that the risk of LOS was significantly lower with antibiotic use, with an adjusted odds ratio of 0.08 (95% CI: 0.01–0.88; p = 0.039). This suggests that administering antibiotics before the onset of sepsis may have a protective effect against developing LOS in preterm infants.[14] In a prior clinical study, the impact of administering antibiotics during the initial 48 h of life on the microbiome of preterm infants was examined in comparison to a control group that did not receive antibiotics.[23] The results of the research indicate that early exposure to antibiotics did not have a detrimental effect on the composition of the microbiome. Noteworthy, there were no notable variances in the overall diversity, richness of species, or beta-diversity of the microbiomes between the preterm infants who were given antibiotics and those who were given a placebo.[23] Moreover, complementary investigations using mouse models revealed no significant distinctions in weight gain, intestinal maturation, or behavior among the offspring colonized with microbiota, thereby reinforcing the outcomes observed in human infants.[23] Similarly, prior studies utilizing preterm pigs as a model demonstrated that prophylactic antibiotics effectively reduced gut bacterial load, enhancing intestinal structure and function, and improved intestinal health by reducing inflammation and enhancing immune function in preterm pigs.[15,24,25]

Limitations

In this meta-analysis, we recognize some limitations. The variability in antibiotic exposure duration is one such factor. Although Egger's test suggests no publication bias, the small number of studies analyzed warrants cautious interpretation. Additionally, despite using multivariable logistic regression

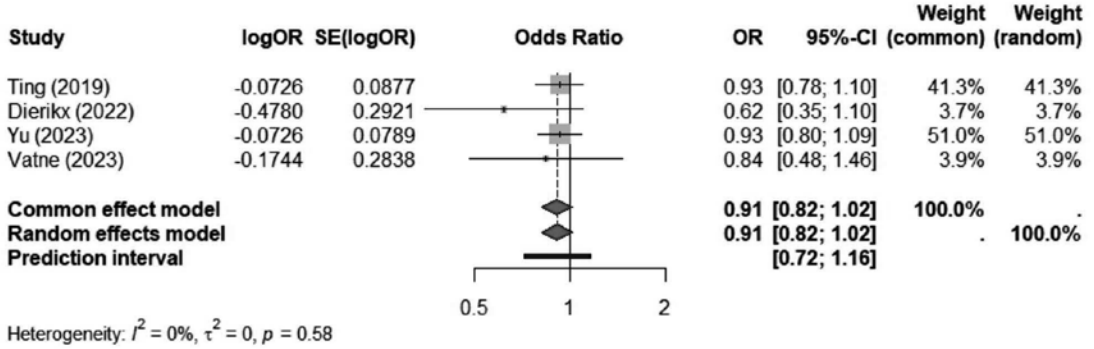

Figure 4. Meta-analysis of the risk of late-onset sepsis in preterm infants exposed to a prolonged course of antibiotics versus non-exposed. This analysis includes four studies with a combined sample size of 41,938 preterm infants.

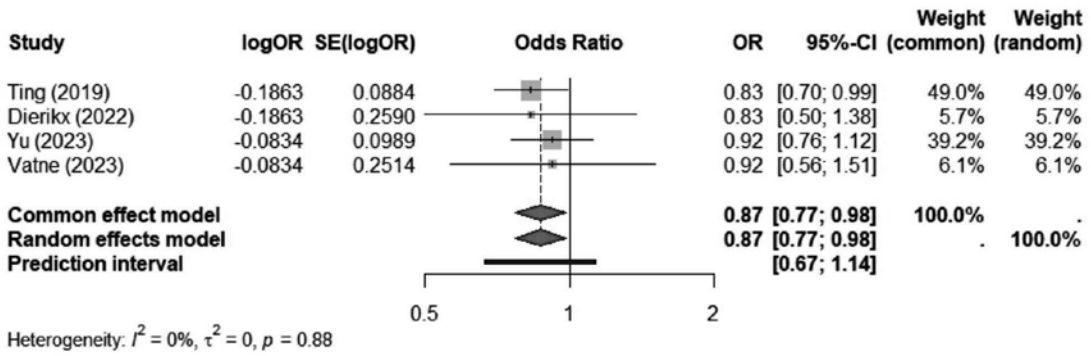

Figure 5. Meta-analysis of late-onset sepsis in preterm infants exposed to a short course of antibiotics versus non-exposed. This analysis includes four studies with a combined sample size of 41,938 preterm infants.

to adjust for confounders, there may still be some residual confounding, as certain factors not included in the models could potentially affect the observed associations. Future research should aim to address these limitations by using standardized definitions, improving study quality, and including larger, more diverse sample sizes.

Conclusion

Our findings indicate that prolonged early antibiotic exposure in preterm infants with sterile cultures does not significantly increase the risk of LOS compared to no antibiotic exposure. Interestingly, a shorter duration of antibiotic exposure might be associated with a slightly lower risk of LOS.

Abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
aOR	Adjusted Odds Ratios
PI	Prediction Interval
NICU	Neonatal Intensive Care Unit
NEC	Necrotizing Enterocolitis
LOS	Late-Onset Sepsis
NOS	Newcastle Ottawa Scale
PROM	Premature Rupture of Membranes
GA	Gestational Age
CRIB	Clinical Risk Index for Babies
SGA	Small for Gestational Age
IUGR	Intrauterine Growth Restriction
PIH	Pregnancy-Induced Hypertension
APH	Antepartum Hemorrhage
Apgar	Appearance, Pulse, Grimace, Activity, Respiration
SNAP-II	Score for Neonatal Acute Physiology
SMA	Small for Gestational Age

Author contributions

AAz created the concept for this study. The following authors YF, HK, handled the retrieval and screening of studies, which were then verified by ME and AAz. Data collection and interpretation were carried out by MA, MK with subsequent verification by AS, MM. Data analysis was conducted by SE, and DA and then reviewed by, AH and AAz. All authors participated in the discussion and the research conclusions. The manuscript was written by AAz with input from all authors. All authors reviewed and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Competing interests

The authors declare no competing interests.

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Measuring Transtracheal Pressure During Passy-Muir Valve Application: Impact on Patient Outcomes

Laura Brooks, MS, CCC-SLP, BCS-S

Introduction

The Passy-Muir® Tracheostomy & Ventilator Swallowing and Speaking Valve (PMV®) is the only bias-closed, no-leak speaking valve, which means that it is the only valve that allows 100% of the exhalation to return through the patient's upper airway when the Valve is placed on a tracheostomy tube hub or in-line in the ventilator circuit. While other speaking valves have a leak and may still allow a patient to vocalize, the design of the Passy-Muir Valve has been shown to restore subglottic pressure for glottic or vocal cord closure.[1-2] This restoration of subglottic pressure not only provides benefits to the patient (coughing, swallowing, bearing down, and restoring intrathoracic pressure), it also allows the clinician to gain insight into the pressure within the trachea when the Passy-Muir Valve is applied. It is critical to know this measurement, as any obstruction compromising exhalation may increase the pressure within the trachea, also known as transtracheal pressure (TTP).

Airway Patency

The airway is separated into the upper and lower airways. The upper airway includes the oral cavity (lips, tongue, jaw, palate), nasopharynx, pharynx, and larynx (glottis). The supraglottis is the area above the vocal cords, the glottis area is the true vocal cords, and the subglottis is the area below the vocal cords. The lower airway includes the trachea and the lungs.

When the PMV is placed on a tracheostomy tube hub or in-line in the ventilator circuit, it can be difficult to determine if the patient can adequately exhale, particularly for infants. Stress signs, whoosh after removal, and coughing with placement of the PMV are subjective signs but are often misleading. The clinician needs to ensure airway patency or opening of the trachea before any negative outcomes, such as oxygen desaturation or bradycardia, are associated with poor tolerance. Measuring transtracheal pressure with PMV application is an objective way to ensure that the pressure intended to remain in the airway, the positive end-expiratory pressure (PEEP), remains the same with the use of the PMV. If the airway is not patent, and there is some level of obstruction at the level of the tracheostomy tube or above, the patient may not be able to tolerate the speaking valve. Measuring TTP has the following benefits, including, but not limited to:

1. Ensuring airway patency when applying the PMV and ensuring patient safety.[3-4]
2. Guiding workup for the causes of high pressures: downsizing the tracheostomy tube if the tracheostomy tube is too large, repeating DLB [direct laryngoscopy and bronchoscopy] for airway evaluation to assess the presence of unknown upper airway obstruction with a need for intervention.
3. Determining readiness for capping trials.
4. Determining readiness for possible decannulation.[5]
5. Identifying complete tracheostomy tube obstruction or complete mucous plug, prompting urgent tracheostomy tube exchange.

Transtracheal pressure. Transtracheal pressure is the pressure within the trachea at the end of exhalation. For a patent (open) airway without obstruction, when a patient is *on* the ventilator, the TTP should read close to the set and delivered PEEP. For ventilator-dependent patients, the PMV is placed in-line (in the ventilator circuit) with the manometer to measure airway patency. (See Figure 1 for PMV and manometer placement in-line with mechanical ventilation) The adapters may vary depending on the ventilator circuit.

Because the PMV allows the patient to receive support "one-way" during inhalation, the PEEP that was *delivered* from the ventilator reached the patient's airway with the PMV in-line. Therefore, the intended set PEEP from the ventilator would be close to the pressure measured within the trachea if the airway is patent. If the airway was not patent, the TTP would increase because the patient had been unable to exhale adequately, and the manometer would reflect a number at the end of exhalation that was higher than the intended PEEP. For example, if the PEEP is set at 5 cm H_2O, the measured TTP would be 5 if the airway is patent. If the measured TTP is higher than 5 then there is some level of obstruction.

Off the ventilator, the pressure at the end of exhalation should ideally read 5 cm H_2O or less. If there was a little resistance, the manometer might read between 0 and 5 cm H_2O, and the patient may still comfortably wear the PMV. TTPs that are

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Figure 1. Transtracheal pressure setup for in-line with mechanical ventilation and PMV use.

higher than 5 cm H_2O may indicate some degree of obstruction, as the inability to adequately exhale increases the pressure within the trachea and causes higher TTP readings.

When the PMV is placed on a tracheostomy tube (no ventilator) and the TTP is 0 cm H_2O (the analog manometer needle does not move), the clinician also should test the manometer by asking the patient to cough or vocalize. If the needle moves, this demonstrates that the manometer is working (see Figures 2 and 3).

If the clinician needs to obtain the exact pressure measurement, a digital manometer is recommended (see Figure 4). This is connected to the adapters in the same way the analog manometer is connected in Figure 1.

The benefits of using TTP are illustrated in the following case study.

Case Study

CS is a 21-month-old male who was born at 24 weeks gestation. His past medical history included severe bronchopulmonary dysplasia (BPD), chronic lung disease (CLD), and tracheostomy with ventilator dependence. He also was briefly admitted for G-tube dislodgement. His LTV ventilator settings were as follows: mode, SIMV, PC/PS; and settings, PIP 18 cm H_2O, PEEP 9 cm H_2O, PS +8 cm H_2O, and tidal volumes ranged 85-110 ml. His tracheostomy tube was a 4.0 cuffed Bivona inflated with 2 ml of water. He was referred for a PMV trial. The PMV was placed in-line, and his TTP increased with every breath up to 30 cm H_2O after < 30 seconds, so the SLP removed the Valve. He was in a calm state, and his TTP was measured with resting breaths. This

Figure 2. Manometer reading with resting breaths.

Figure 3. Manometer reading during vocalizations.

indicated likely some upper airway obstruction compromising his ability to exhale with the PMV in-line.

Three months later, he had a direct laryngoscopy and bronchoscopy (DLB) during which the ENT found a completely obstructive suprastomal granuloma which was then removed. He was seen one month later for a Videofluoroscopic Swallow Study. The pulmonologist agreed to have the SLP retest TTP with the PMV. There was an improvement in TTP to 15 cm H_2O but still higher than his PEEP, indicating some level of obstruction. He could not be cleared for PMV use at that time, but ENT planned to take him back to the OR for a repeat DLB in a few months. PMV trials were ongoing at outpatient pulmonology clinic visits and with SLP visits.

Teaching Points for the Case Study

Vent. LTV ventilator is a home ventilator.

Ventilator settings. Mode of SIMV PC/PS and settings of PIP 18 cm H_2O, PEEP of 9 cm H_2O, PS +8 cm H_2O, and tidal volumes

Figure 4. Digital manometer may be used for more precise measurements.

ranging 85-110 ml. His mode of ventilation was SIMV, pressure control, and pressure support. Synchronized Intermittent Mandatory Ventilation with Pressure Support (SIMV/PS) tends to be a very comfortable mode for patients. The ventilator delivers a predetermined number of breaths per minute, and pressure support can be provided during spontaneous breathing. In pressure control mode, the pressure is set (PIP = 18 cm H_2O) and the volume is variable (TV range 85-110 ml). Pressure support is the support that the ventilator provides when the patient takes a breath, and his peak inspiratory pressure (PIP) is the PS value + PEEP value. In his case, a PS of 8 cm H_2O and PEEP of 9 cm H_2O equaled a PIP of 17 cm H_2O. Note that his PIP (PS + PEEP) for his spontaneous breaths is close to his set PIP for his ventilator breaths: 17, 18, respectively.

TTP on the ventilator. Should be consistent with the set PEEP if the airway is patent. A discrepancy between his TTP and his PEEP indicated some level of obstruction. This could be due to upper airway obstruction (oral, nasal, pharyngeal, laryngeal) or at the level of the tracheostomy tube. The ENT would consider downsizing if the DLB did not reveal any other upper airway obstruction. In his case, his ENT planned to take him back to the OR for a DLB in a few months.

When considering the use of TTP to evaluate airway patency, the TTP measurement ranges, for both on and off the ventilator provide an indication of how patent the airway is. This patency may impact considerations for use of the PMV. The following tables provide an overview of the TTP measurements ranges:

If the patient is ON a ventilator:

Resting TTP ≤ 10 cm H_2O Likely to pass: (consistent with PEEP delivered).	TTP 10-14 borderline- may tolerate PMV but patient specific.	TTP 15-20 likely too high but patient specific.	Resting TTP > 20 cm H_2O. Likely to be unable to use a speaking valve.
Action: Proceed with PMV trial.	• Start with SLP as tolerated • Closely monitor for work of breathing or stress signs.	• Strict monitoring by SLP. • Closely monitor for work of breathing or stress signs. • May need cuffless tracheostomy tube or downsizing of tracheostomy tube.	• Review possible confounding effects, such as obstruction, large tracheostomy tube, and more. • Consider contacting ENT. • Next steps may include visual assessment of upper airway or downsizing tracheostomy tube.

If the patient is OFF the ventilator:

Resting TTP < 5 cm H_2O. Likely to pass.	TTP 5-10 borderline may tolerate PMV but patient specific.	TTP 10-15 likely too high but patient specific.	Resting TTP > 15 cm H_2O. Likely to be unable to use a speaking valve.
Action: Proceed with PMV trial.	• Start with SLP as tolerated. Closely monitor for work of breathing or stress signs.	• Strict monitoring by SLP. • Closely monitor for work of breathing or stress signs. • Contact ENT. • Next steps may include assessment of upper airway (DLB), downsizing tracheostomy tube, or changing to cuffless tracheostomy tube.	• Review possible confounding effect, obstruction, large tracheostomy tube. • Contact ENT. • Next steps may include assessment of upper airway, downsizing tracheostomy tube, or changing to cuffless tracheostomy tube.

Summary

Using TTP provides an objective measure to ensure that airway patency is sufficient for PMV use. When considering the needs of patients with tracheostomies, the PMV restores a more normal closed system, which allows for airflow through the upper airway and may impact vocalizations, feeding and swallowing, trunk support, and more. The case study illustrated the benefits of objectively measuring transtracheal pressure to ensure airway patency for tracheostomy-dependent patients on and off the ventilator. Measuring TTP when using the PMV has the potential to positively impact patient outcomes and safety.

Children's Healthcare of Atlanta Institutional Review Board approved this project, IRB number STUDY00002271.

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Maternal Obesity and the Incidence of Large-for-Gestational-Age Newborns in Isolated Hypothyroxinemia Pregnancies: A Comparative Cohort Study

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Abstract

Background

The synergistic impact of isolate maternal hypothyroxinaemia (IMH) and other modulators on fetal growth outcomes is unknown. This study was aimed to determine whether third trimester IMH [free thyroxine level (FT4) below the the 5th percentile and thyroid stimulating hormone (TSH) between the 5th and 95th percentiles] and prenatal body mass index (BMI) jointly increase the risk of large for gestational age (LGA) deliveries.

Methods

A retrospective analysis was conducted on 11,478 Chinese pregnant women with laboratory data (including thyroid hormone levels and routine biochemical tests) and hospitalization records from a specialized hospital.

Results

The prevalence of obesity (BMI ≥ 30 kg/m^2) and IMH was 20.1% (2312/11478) and 4.5% (519/11478), retrospectively. Women with obesity had a 6.96-fold greater risk of IMH (95% CI: 4.58, 10.58) and a 5.88-fold increased risk of LGA (95% CI: 4.87, 7.11) than those with normal weight (BMI < 25 kg/m^2), while women with IMH had a 1.32-fold increased risk of LGA (95% CI: 1.05, 1.65) than euthyroid women. The positive associations of LGA risk with obesity and IMH remained robust in sensitivity analyses conducted among women aged < 35 years, primiparas, and those without pregnancy complications. Compared to euthyroid women with normal weight, women with obesity and IMH had a 7.60-fold higher risk of LGA (95% CI: 5.26, 10.97). Additionally, a significant interaction between BMI categories and IMH on LGA was observed (P < 0.013). Subgroup analyses validated this interaction among women with aged < 35 years, multiparity, and non-pregnancy complications.

Conclusions

Obesity and IMH in late pregnancy are both associated with an increased risk of LGA newborns, and their coexistence may further amplifies this risk; prenatal BMI and thyroid hormone levels could serve as potential indicators for identifying individuals at elevated LGA risk.

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Introduction

Birth weight is a key indicator of fetal growth and has long-term health implications, as highlighted by the developmental origins of health and disease theory.[1] Newborns classified as large for gestational age (LGA, > 90th percentile) or small for gestational age (SGA, < 10th percentile) face increased risks of adverse outcomes.[2,3] LGA infants are more prone to obesity, diabetes, cardiovascular issues, and certain cancers, while SGA infants are at higher risk of neurodevelopmental disorders, metabolic dysfunction, and hepatic tumors.[4-6] The prevalence of LGA has risen in developed countries, whereas SGA rates have increased in developing nations.[2] Interventions to prevent SGA and LGA are crucial for improving neonatal health and promoting socioeconomic development.

Thyroid hormones are vital for fetal development, especially before 20 weeks of gestation when the fetus depends on maternal thyroid hormones.[7,8] Maternal thyroid dysfunction, particularly isolated maternal hypothyroxinemia (IMH), has garnered increasing attention due to its potential impact on fetal growth.[9] While overt maternal hyperthyroidism and hypothyroidism are linked to low birth weight, the effects of IMH on birthweight remain controversial.[10] Most studies associate first- or second-trimester IMH with increased birthweight, macrosomia, or LGA,[11-17] while a few suggest a link to lower birthweight (LBW) and SGA.[18-20] Other studies find no significant correlation between IMH and fetal growth outcomes, underscoring the need for further research to clarify these relationships.[21-27]. Given the critical role of maternal thyroid function in late pregnancy on fetal thyroid status, there is a pressing need for research focusing on isolated maternal hypothyroxinemia (IMH) during this period.[28] This retrospective study aimed to determine whether IMH in late pregnancy increases the prevalence of SGA or LGA newborns among Chinese women. Additionally, since maternal weight at delivery is a known determinant of fetal birth weight,[29,30] we explored the potential synergistic effects

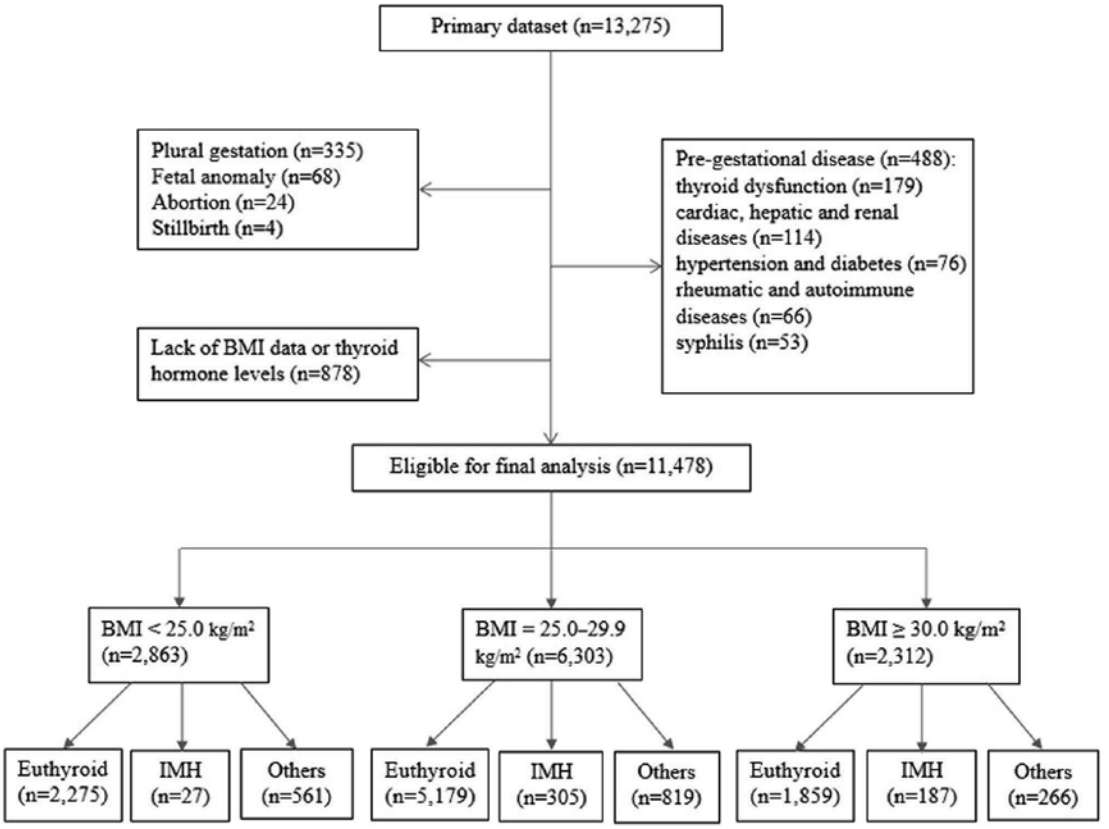

Figure 1. Flow diagram.

of IMH and prenatal body weight status on fetal growth outcomes.

Materials and methods

Data source and study design

Utilizing the comprehensive data repository sourced from Changzhou Maternal and Child Health Care Hospital, we performed this retrospective, observational cohort study. The research protocol was reviewed and approved by the Ethics Committee of the hospital, with approval number ZD201803. Given the anonymous nature of the data used in this study, the requirement for informed consent from individual participants was waived. The original database comprised 13,275 consecutive subjects who delivered babies in the hospital from the start of April 2016 to the end of March 2017. During this timeframe, free thyroid testing (funded by the reagent supplier and hospital research grants) was widely adopted by pregnant women admitted for delivery, enabling robust data collection. Outside this period, testing required fees, limiting accessibility. The 12-month window provided sufficient sample size to detect associations between IMH and LGA/SGA while minimizing seasonal variability in maternal behaviors. The following criteria were used for excluding participants from the final analysis: (i) history of pre-pregnancy illnesses that may modulate thyroid hormone levels and affect subsequent birth outcomes, including thyroid disease, chronic conditions (hypertension, heart, liver and kidney diseases), diabetes mellitus, syphilis and immune rheumatic disease; (ii) harmful habits during pregnancy (smoking, drinking alcohol, and using illegal drugs); (iii) multiple pregnancy; (iv) failure of live birth; (v) absence of thyroid function assessment and height/weight measurement. A total of 1,797 participants who presented with a history of pre-pregnancy diseases (n = 488), plural gestations (n = 335), congenital malformations (n = 68), non-live birth (n = 28), and missing thyroid hormones levels and height/weight values (n = 878) were ultimately excluded from the current study (Fig. 1). Data regarding to maternal demographics and neonatal characteristics, such as maternal age, height, weight, parity status, blood pressure (BP), medical history, harmful habits, pregnancy complications, fetal sex, gestational week at delivery, as well as birth length and weight of the neonates, were meticulously checked and retrieved from the hospital's medical records. The results of thyroid function tests and other routine laboratory assessments conducted upon admission to the hospital were comprehensively reviewed and extracted from the hospital's laboratory information system.

Laboratory measurements and definition of thyroid function

Maternal blood samples were collected at the time of admission for hospital delivery and transferred to the laboratory for subsequent thyroid function testing and biochemical analysis. Serum free triiodothyronine (FT3), free thyroxin (FT4), thyroid-stimulating hormone (TSH) and thyroid peroxidase antibody (TPO-Ab) were assayed utilizing the electrochemiluminescence technique on an automated immunoassay analyzer (Cobas Elecsys 601, Roche Diagnostics, Switzerland). Routine measurements of serum liver and kidney function, as well as whole blood cell counts, were conducted utilizing advanced automatic analyzers and their respective, suitable reagents. For liver and kidney function evaluations, the AU5800 analyzer from Beckman Coulter Inc. (Japan) was employed, while for blood cell counts, the XN550 analyzer from Sysmex Inc. (Japan) was utilized. Based on the manufacturer's specifications, a TPO-Ab

Table 1 Descriptive statistics for characteristics of the study population ($n = 11,478$)

Characteristics	Normal weight ($n = 2,863$)	Overweight ($n = 6,303$)	Obesity ($n = 2,312$)	*P* value
Age (years)	27.7 ± 4.0	28.8 ± 4.4	29.2 ± 4.7	< 0.001
<35	2656 (92.8%)	5535 (87.8%)	1973 (85.3%)	< 0.001
≥35	207 (7.2%)	768 (12.2%)	339 (14.7%)	
Height (cm)	161.8 ± 4.6	161.6 ± 4.6	161.4 ± 4.6	0.001
Weight (kg)	61.4 ± 4.8	71.2 ± 5.4	84.4 ± 7.6	< 0.001
BMI (kg/m^2)	23.4 ± 1.2	27.3 ± 1.4	32.4 ± 2.2	< 0.001
Systolic BP (mmHg)	118.5 ± 10.7	120.8 ± 11.6	124.6 ± 13.8	< 0.001
Diastolic BP (mmHg)	73.3 ± 7.6	74.4 ± 8.0	76.5 ± 9.4	< 0.001
Parity				
No child	1926 (67.3%)	3725 (59.1%)	1252 (54.2%)	< 0.001
≥1 child	937 (32.7%)	2578 (40.9%)	1060 (45.8%)	
Gestational age (week)	38.6 ± 1.8	38.8 ± 1.5	38.7 ± 1.6	0.010
Assisted reproduction	41 (1.4%)	144 (2.3%)	77 (3.3%)	< 0.001
Delivery mode				
Vaginal delivery	1933 (67.5%)	3629 (57.6%)	1027 (44.4%)	< 0.001
Cesarean section	930 (32.5%)	2674 (42.4%)	1285 (55.6%)	
PTB	241 (8.4%)	366 (5.8%)	149 (6.4%)	< 0.001
Pregnancy complications				
GDM	174 (6.1%)	494 (7.8%)	295 (12.8%)	< 0.001
ICP	208 (7.3%)	371 (5.9%)	130 (5.6%)	0.018
PE	38 (1.3%)	174 (2.8%)	180 (7.8%)	< 0.001
PIH	21 (0.7%)	112 (1.8%)	110 (4.8%)	< 0.001
IMH	27 (0.9%)	305 (4.8%)	187 (8.1%)	< 0.001
Neonatal sex				
Female	1370 (47.9%)	2948 (46.8%)	1093 (47.3%)	0.624
Male	1493 (52.1%)	3355 (53.2%)	1219 (52.7%)	
Neonatal birth height (cm)	49.6 ± 1.6	49.9 ± 1.2	50.0 ± 1.4	< 0.001
Neonatal birth weight (gram)	3159.3 ± 462.6	3368.5 ± 463.3	3517.9 ± 527.4	< 0.001
Weight for gestational age				
SGA	444 (15.5%)	463 (7.3%)	105 (4.5%)	< 0.001
AGA	2241 (78.3%)	4884 (77.5%)	1560 (67.5%)	
LGA	178 (6.2%)	956 (15.2%)	647 (28.0%)	
Laboratory findings				
FT3 (pmol/L)	3.9 ± 0.6	4.1 ± 0.6	4.2 ± 0.6	< 0.001
FT4 (pmol/L)	13.5 ± 1.9	12.6 ± 1.8	12.1 ± 1.9	< 0.001
TSH (mIU/L)	3.1 ± 1.9	3.0 ± 1.7	3.9 ± 1.6	< 0.001
TPO-Ab (mIU/L)	17.7 ± 34.1	17.3 ± 30.6	18.5 ± 33.9	0.191
RBC (10^{12}/L)	4.0 ± 0.4	4.0 ± 0.3	4.1 ± 0.4	< 0.001
WBC (10^9/L)	8.7 ± 2.2	8.8 ± 2.2	8.8 ± 2.2	0.070
Platelet (10^9/L)	197.0 ± 54.0	202.9 ± 55.5	209.6 ± 56.5	< 0.001
Hemoglobin (g/L)	118.1 ± 11.8	118.7 ± 11.9	120.0 ± 11.7	< 0.001
Total bilirubin (μmol/L)	8.2 ± 3.3	7.9 ± 2.9	7.5 ± 2.8	< 0.001
Direct bilirubin (μmol/L)	1.7 ± 1.1	1.6 ± 1.0	1.5 ± 0.9	< 0.001
ALT (U/L)	12.0 ± 16.2	11.2 ± 11.6	11.8 ± 15.0	0.041
AST (U/L)	20.9 ± 12.2	19.7 ± 9.4	20.4 ± 28.6	0.003
Total protein (g/L)	64.0 ± 4.5	63.6 ± 4.3	62.9 ± 4.2	< 0.001
Albumin (g/L)	36.9 ± 2.5	36.5 ± 2.5	35.9 ± 2.5	< 0.001
Urea nitrogen (mmol/L)	3.6 ± 1.0	3.5 ± 0.9	3.5 ± 0.9	0.310
Creatinine (umol/L)	60.4 ± 8.8	60.2 ± 8.9	59.9 ± 9.6	0.142

BMI, body mass index; BP, blood pressure; PTB, preterm birth; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PE, preeclampsia; PIH, pregnancy induced hypertension; IMH, isolated maternal hypothyroxinaemia; SGA/AGA/LGA, small/appropriate/large for gestational age; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TPO-Ab, thyroid peroxidase antibody; RBC, red blood cells; WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

level exceeding 34.0 mIU/L was designated as positive. According to the percentiles distribution of FT4 and TSH levels among participants with negative TPO-Ab status, maternal thyroid function was categorized as follows: Euthyroid, normal TSH and FT4 (5th-95th percentiles); hypothyroxinaemia, normal TSH and low FT4 (< 5th percentile); hypothyroidism, normal/low FT4 FT4 and high TSH (> 95th percentile); hyperthyroxinaemia, normal TSH and high FT4; and hyperthyroidism, normal/high FT4 and low TSH. Due to the lack of manufacturer-provided trimester-specific reference ranges for TSH/FT4, we established regional

Table 2 Association of BMI with thyroid hormone levels and IMH

	FT3 (pmol/L)		FT4 (pmol/L)		TSH (mIU/L)		IMH	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
Normal weight	0		0		0		1	
Overweight	0.11 (0.09, 0.14)	< 0.001	-0.89 (-0.97, -0.81)	< 0.001	-0.13 (-0.20, -0.05)	0.002	4.96 (3.34, 7.38)	< 0.001
Obese	0.25 (0.21, 0.28)	< 0.001	-1.37 (-1.47, -1.27)	< 0.001	-0.24 (-0.34, -0.14)	< 0.001	8.48 (5.64, 12.75)	< 0.001
Per-1 kg/m^2 increase	0.03 (0.02, 0.03)	< 0.001	-0.15 (-0.16, -0.14)	< 0.001	-0.03 (-0.04, -0.02)	< 0.001	1.16 (1.13, 1.18)	< 0.001
Model 2								
Normal weight	0		0		0		1	
Overweight	0.11 (0.08, 0.13)	< 0.001	-0.79 (-0.87, -0.71)	< 0.001	-0.11 (-0.19, -0.03)	0.005	4.63 (3.10, 6.91)	< 0.001
Obese	0.21 (0.18, 0.25)	< 0.001	-1.20 (-1.31, -1.10)	< 0.001	-0.24 (-0.34, -0.14)	< 0.001	6.96 (4.58, 10.58)	< 0.001
Per-1 kg/m^2 increase	0.02 (0.02, 0.03)	< 0.001	-0.13 (-0.14, -0.12)	< 0.001	-0.03 (-0.04, -0.02)	< 0.001	1.13 (1.10, 1.16)	< 0.001

Model 1 was unadjusted. Model 2 was adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; TPO-Ab, thyroid peroxidase antibody.

Table 3 Association of BMI and IMH with fetal growth and SGA/LGA risk

	Birth length		Birth weight		SGA		LGA	
	β (95% CI)	*P* value	β (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Model 1								
Normal weight	0		0		1		1	
Overweight	0.26 (0.20, 0.32)	< 0.001	212.91 (192.16, 233.67)	< 0.001	0.44 (0.38, 0.50)	< 0.001	2.74 (2.33, 3.22)	< 0.001
Obese	0.39 (0.31, 0.46)	< 0.001	360.26 (334.52, 386.00)	< 0.001	0.26 (0.21, 0.33)	< 0.001	5.80 (4.88, 6.89)	< 0.001
Per-1 kg/m^2 increase	0.04 (0.03, 0.05)	< 0.001	39.45 (36.92, 41.98)	< 0.001	0.84 (0.82, 0.86)	< 0.001	1.18 (1.17, 1.20)	< 0.001
Euthyroid	0		0		1		1	
IMH	0.01 (-0.11, 0.14)	0.839	43.54 (0.15, 86.93)	0.049	0.90 (0.65, 1.24)	0.516	1.41 (1.14, 1.76)	0.002
Model 2								
Normal weight	0		0		1		1	
Overweight	0.14 (0.09, 0.18)	< 0.001	167.01 (150.14, 183.88)	< 0.001	0.40 (0.35, 0.47)	< 0.001	2.67 (2.24, 3.17)	< 0.001
Obese	0.30 (0.24, 0.36)	< 0.001	323.96 (302.24, 345.68)	< 0.001	0.19 (0.15, 0.25)	< 0.001	5.88 (4.87, 7.11)	< 0.001
Per-1 kg/m^2 increase	0.04 (0.03, 0.04)	< 0.001	37.79 (35.63, 39.95)	< 0.001	0.81 (0.79, 0.83)	< 0.001	1.20 (1.18, 1.22)	< 0.001
Euthyroid	0		0		1		1	
IMH	0.10 (-0.00, 0.19)	0.052	53.29 (18.89, 87.69)	0.002	0.79 (0.56, 1.11)	0.169	1.32 (1.05, 1.65)	0.019

Model 1 was unadjusted. Model 2 was adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; SGA/LGA, small/large for gestational age; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

thresholds using our laboratory's pregnancy-specific thyroid hormone data. The 5th-95th percentile cutoffs were selected to align with current evidence and ensure comparability with prior studies, thereby supporting standardized clinical decisions,[31] and to optimize clinical practicality. Narrower cutoffs (10th-90th percentiles) risk overdiagnosing mild hypothyroxinemia in iodinesufficient populations, potentially leading to unnecessary interventions, while broader cutoffs (2.5th-97.5th percentiles) reduce sensitivity and increase the risk of missed diagnoses. By contrast, the 5th-95th percentiles strike a balance between specificity and sensitivity, minimizing the misclassification of transient or subclinical deviations while effectively detecting clinically significant abnormalities.

Definitions of covariates and outcomes

Maternal age was dichotomized into two categories: ≥35 years and < 35 years. Additionally, maternal prenatal body mass index (BMI) was stratified into three distinct groups: normal weight (BMI < 25 kg/m^2), overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) [32]. Pre-eclampsia (PE), pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), and intrahepatic cholestasis of pregnancy (ICP) were recognized as pivotal complications during gestation, with their diagnoses relying on well-established criteria outlined in a previous report [33]. The newborns were stratified into three categories based on their birthweight and gestational week, employing the methodology devised by Mikolajczyk: (i) SGA, identified by a birthweight falling below the 10th percentile of the gestational age-specific reference range within the study cohort; (ii) AGA, characterized by a birthweight lying within the 10th to 90th percentile; (iii) LGA, designated by a birthweight exceeding the 90th percentile [2]. To establish reference percentiles, the cohort-specific mean birthweight (3513.8 g) and standard deviation (SD: 402.3 g) for term infants (40 weeks) were first calculated. The coefficient of variation (CV = 11.45%) was then derived as (SD/mean)×100. These parameters were input into a predefined Microsoft Excel algorithm (Web Appendix 2),[2] which generated continuous birthweight percentiles across gestational ages from 24 to 41 weeks, ensuring age-specific classification accuracy.

Statistical analysis

Data were presented as mean (standard deviation, SD) for continuous variables, and as frequency (percentage) for categorical variables. The pregnant women were stratified into three groups based on the categories of prenatal BMI at

Table 4 Modification effect of BMI on associations between IMH and LGA neonates

	Euthyroid		IMH		Crude		*P* value [a] for Interaction	Adjusted [b]		*P* value [a] for Interaction
	Total	LGA (%)	Total	LGA (%)	OR (95% CI)	*P* value		OR (95%CI)	*P* value	
Normal weight	2275	147 (6.5%)	27	5 (18.5%)	3.29 (1.23, 8.81)	0.018		2.86 (1.01, 8.12)	0.048	
Overweight	5179	794 (15.3%)	305	38 (12.5%)	2.06 (1.41, 3.01)	< 0.001		2.00 (1.36, 2.96)	< 0.001	
Obese	1859	512 (27.5%)	187	64 (34.2%)	7.53 (5.33, 10.64)	< 0.001	0.009	7.60 (5.26, 10.97)	< 0.001	0.013

[a] Interaction test for BMI (normal weight vs. Overweight/obese) and IMH (euthyroid vs. IMH) on LGA risk. [b] Adjusted for adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; LGA, large for gestational age; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

Table 5 Subgroup analysis of modified effect of BMI on associations between IMH and LGA neonates

	Euthyroid		IMH		Crude		*P* value [a] for Interaction	Adjusted [b]		*P* value [a] for Interaction
	Total	LGA (%)	Total	LGA (%)	OR (95% CI)	*P* value		OR (95%CI)	*P* value	
Age < 35 years										
Normal weight	2101	131 (6.2%)	22	4 (18.2%)	3.34 (1.11, 10.02)	0.031		3.59 (1.17, 11.07)	0.026	
Overweight	4566	649 (14.2%)	251	28 (11.2%)	1.89 (1.23, 2.91)	0.004		1.96 (1.26, 3.05)	< 0.001	
Obese	1581	411 (26.0%)	153	51 (33.3%)	7.52 (5.14, 10.99)	< 0.001	0.013	7.78 (5.19, 11.66)	< 0.001	0.015
Age ≥ 35 years										
Normal weight	174	16 (9.2%)	5	1 (20.0%)	2.47 (0.26, 23.44)	0.431		1.72 (0.16, 19.05)	0.658	
Overweight	613	145 (23.7%)	54	10 (18.5%)	2.24 (0.95, 5.29)	0.065		2.66 (1.09, 6.45)	0.031	
Obese	278	101 (36.3%)	34	13 (38.2%)	6.11 (2.58, 14.47)	< 0.001	0.547	7.60 (3.04, 19.04)	< 0.001	0.661
Primipara										
Normal weight	1513	70 (4.6%)	16	1 (6.2%)	1.37 (0.18, 10.55)	0.760		1.51 (0.19, 11.77)	0.694	
Overweight	3045	353 (11.6%)	188	22 (11.7%)	2.73 (1.65, 4.53)	< 0.001		2.74 (1.63, 4.59)	< 0.001	
Obese	999	239 (23.9%)	103	29 (28.2%)	8.08 (4.94, 13.21)	< 0.001	0.801	7.50 (4.46, 12.62)	< 0.001	0.877
Multipara										
Normal weight	762	77 (10.1%)	11	4 (36.4%)	5.08 (1.46, 17.76)	0.011		4.11 (1.12, 15.12)	0.033	
Overweight	2134	441 (20.7%)	117	16 (13.7%)	1.41 (0.79, 2.51)	0.244		1.29 (0.71, 2.32)	0.405	
Obese	860	273 (31.7%)	84	35 (41.7%)	6.35 (3.88, 10.41)	< 0.001	0.002	6.45 (3.83, 10.88)	< 0.001	0.003
NPC										
Normal weight	1952	123 (6.3%)	23	5 (21.7%)	4.13 (1.51, 11.31)	0.006		3.97 (1.36, 11.63)	0.012	
Overweight	4324	633 (14.6%)	248	29 (11.7%)	1.97 (1.28, 3.02)	0.002		1.98 (1.27, 3.07)	0.002	
Obese	1387	345 (24.9%)	123	42 (34.1%)	7.71 (5.09, 11.68)	< 0.001	0.003	7.63 (4.93, 11.82)	< 0.001	0.006

[a] Interaction test for BMI (normal weight vs. Overweight/obese) and IMH (euthyroid vs. IMH) on LGA risk. [b] Adjusted for adjusted for age, parity, BP, gestational age, assisted reproduction, pregnancy complications, neonatal sex, and laboratory findings (WBC, RBC, platelet, hemoglobin, hepatic and renal function, FT3, and TPO-Ab status). BMI, body mass index; IMH, isolated maternal hypothyroxinaemia; LGA, large for gestational age; NPC, non-pregnancy complications; CI, confidence interval; OR, odds ratio; RBC, red blood cell; WBC, white blood cell; FT3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibody.

the time of admission. Difference across groups were tested by ANOVA/Kruskal Wallis tests for continuous variables, and Chi-square/Fisher's exact tests for categorical variables. Spearman's correlation test was employed to examine the relationships between maternal BMI and thyroid hormone levels. Linear regression models, tailored for continuous variables, and logistic regression models, designed specifically for dichotomous outcomes, were applied to evaluate the associations of BMI (continuous and categorized) with thyroid hormone levels and IMH. Furthermore, these models were leveraged to calculate both regression coefficients (β) and odds ratios (OR) to quantify the impact of various indexes (BMI, BMI categories and IMH) on birth length, birthweight, as well as SGA/LGA risk. To validate the robustness of the observed associations, sensitivity analyses utilizing logistic regression models were conducted exclusively among participants without advanced age, multipara, or pregnancy complications. Adjusted covariates in the regression analyses included maternal age, parity, blood pressure (BP), gestational week, assisted reproduction, pregnancy complications, fetal sex, and laboratory findings (routine blood tests, hepatic and renal function, FT3, and TPO-Ab status). Similarly, the ORs of LGA across each subgroup classified by BMI categories and euthyroid/IMH status were calculated, and their potential interactions were investigated. Additionally, these interactions were validated in subgroup analyses stratified by maternal clinical characteristics.

Statistical analyses were performed using R (http://www.R-project.org) and Empower Stats (X&Y Solutions, Inc. Boston, Massachusetts), and statistical significance was determined by a *P*-value threshold of less than 0.05.

Results

Participants' characteristics

The process of participants' screening is depicted in Fig. 1. The final analysis comprised 11,478 consecutive subjects. Among these pregnant women, the mean (standard deviation, SD) age at the time of admission for labor was 28.6 (4.4) years old, with a majority of 6,903 individuals (60.1%) being primipara. The prevalence of pregnancy complications was 8.4% for GDM, 6.2% for ICP, 3.4% for PE, and 2.1% for PIH, respectively. In addition, 4.5% (519) of mothers were defined as IMH. Of the 11,478 singleton neonates, 15.5% (1781) were defined as LGA and 8.8% (1012) as SGA. The mean prenatal BMI in our study was 27.3 (SD 3.4) kg/m^2, with 20.1% (2312) being obesity.

The participants were assigned into three groups according to BMI categories (normal weight, overweight, and obesity, Table 1). A significant step-wise increase among BMI categories was observed in terms of maternal age, blood pressure (BP), multipara rate, assisted reproduction rate, cesarean section rate, the prevalence of GDM, PE, and PIH, fetal birth length and weight, platelet counts, and the levels of hemoglobin and FT3. On the contrary, the opposite findings were detected in the variables of FT4, total bilirubin, direct bilirubin, total protein, and albumin. Notably, a positive relationship of BMI categories with IMH prevalence and the incidence of LGA deliveries was found (0.9% and 6.2% in normal weight group, and increased to 4.8% and 15.2% in overweight group, and 8.1% and 28.0% in obesity group). In addition, there was a negative relationship between BMI categories and SGA incidence (15.5% in normal weight group, and decreased to 7.3% and 4.5% in overweight and obesity groups).

Relationships of BMI with thyroid hormone levels and IMH

The distribution of thyroid hormone levels grouped by maternal TPO-Ab status is shown in Table S1. Among the 11,478 mothers with singleton, 5.6% (640), 4.5% (519), 4.8% (547), 4.4% (501), and 4.8% (547) of mothers were defined as TPO-Ab positive, hypothyroxinaemia, hypothyroidism, hyperthyroxinaemia, and hyperthyroidism, respectively. Spearman's correlation analysis revealed significant negative correlation of BMI with TSH (r = -0.044, $P < 0.001$) and FT4 (r = -0.279, $P < 0.001$) levels and positive correlation between BMI and FT3 levels (r = 0.169, $P < 0.001$) in late pregnancy. Regression coefficients for thyroid hormone levels associated with BMI categories are presented in Table 2. Adjusted linear regression models displayed that a 1-kg/m^2 increase in BMI during late pregnancy was associated with a 0.13-pmol/L decrease in FT4 level (95% CI:–0.14,–0.12), a 0.03-mIU/L decrease in TSH level (95% CI:–0.04,–0.02), and a 0.02-pmol/L increase in FT3 level (95% CI: 0.02, 0.03). In comparison to women with a normal weight, overweight and obesity respectively exhibited decreased median levels of FT4 by 0.79 (95% CI: -0.87, -0.71) pmol/L and 1.20 (95% CI: -1.31, -1.10) pmol/L and TSH by 0.11 (95% CI: -1.31, -1.10) mIU/L and 0.24 (95% CI: -0.34, -0.14) mIU/L and increased median levels of FT3 by 0.11 (95% CI: 0.08, 0.13) pmol/L and 0.21 (95% CI: 0.18, 0.25) pmol/L (all $P < 0.001$). In addition, women with obesity had a remarkably higher risk of IMH compared to those of normal weight (crude OR: 8.48, 95% CI: 5.64, 12.75; adjusted OR: 6.96, 95% CI: 4.58, 10.58).

Association of BMI and IMH with fetal growth and SGA/LGA risk

As shown in Table 3, maternal BMI in overweight and obese categories was associated with higher birth length and weight relative to normal-weight category with approximate mean increases of 0.14 cm (95% CI: 0.09, 0.18) and 167.01 g (95% CI: 150.14, 183.88), and 0.30 cm (95% CI: 0.24, 0.36) and 323.96 g (95% CI: 1302.24, 345.68), respectively. Obesity conferred an increased LGA risk and a decreased SGA risk relative to normal weight in both the unadjusted (OR for LGA: 5.80, 95% CI: 4.88, 6.89; OR for SGA: 0.26, 95% CI: 0.21, 0.33) and adjusted logistic regression models (OR for LGA: 5.88, 95% CI: 4.87, 7.11; OR for SGA: 0.19, 95% CI: 0.15, 0.25). Additionally, IMH also increased the birthweight (crude β: 43.54, 95% CI: 0.15, 86.93; adjusted β: 53.29, 95% CI: 18.89, 87.69) and was positively associated with LGA risk (crude OR: 1.41, 95% CI: 1.14, 1.76; adjusted OR: 1.32, 95% CI:1.05, 1.65). The robustness of these associations were demonstrated in sensitivity analyses among the participants with non-advanced age (Table S2), primipara (Table S3), and non-pregnancy complications (Table S4).

Joint effect of obesity and IMH on LGA risk

Table 4 presents the modified effects of BMI categories on the association between IMH and LGA risk. The lowest prevalence of LGA (6.5%) was observed in participants with normal weight and euthyroid, whereas the highest prevalence (34.2%) was observed in those with obesity and IMH, representing a 7.6-fold increase in LGA risk (adjusted OR: 7.60; 95% CI: 5.26, 10.97). Interaction tests between BMI categories and IMH on LGA yielded statistically significant results (crude P for interaction: 0.009; adjusted P for interaction: 0.013). In addition, consistent interactions were detected in these subgroups (non-advanced age, multipara, and non-pregnancy complications; Table 5).

Discussion

Main findings

To the best of our knowledge, this is the largest retrospective study to date, revealing a significant link between prenatal BMI, thyroid hormone, and the risk of LGA deliveries. We observed a positive relationship between BMI categories (normal weight, overweight, and obesity) and the incidence of IMH, which was 0.9% in normal weight, and increased to 4.8% in overweight and 8.1% in obesity. With the elevation of BMI categories, FT3 increased by 0.11 and 0.21 pmol/L, FT4 decreased by 0.79 and 1.20 pmol/L. Additionally, there were significant differences in the risk of LGA deliveries across subgroups classified by BMI categories and euthyroid/IMH status. The lowest incidence of LGA (6.5%) was found in the subgroup with low BMI category (normal weight) and euthyroid, whereas the highest incidence (34.2%) was observed in the subgroup with high BMI category (obesity) and IMH, representing that the absolute risk of LGA increased by 27.8% and the OR increased by 7.6-fold (95% CI: 5.26, 10.97; P for interaction = 0.013). A similar interaction was validated in participants with non-advantage age, multipara, and non-pregnancy complications. Taken together, these findings indicated that women with obesity and IMH in late pregnancy had a higher risk of LGA, emphasizing the importance of tailored clinical settings and management for them.

Interpretation

Previous epidemiological investigations have examined potential alterations in birth weight associated with IMH. Su et al. found that newborns born to mothers with IMH during the initial 20 weeks of pregnancy are at an increased risk of SGA (adjusted OR: 3.55) among 1,017 Chinese women.[18] Nazarpour et al. and Sankoda et al. also observed an increased likelihood of LBW (adjusted OR = 2.53) in 1,843 Iranian women and of SGA (adjusted OR = 12.51) in 1,105 Japanese women, respectively, who were identified as IMH during early pregnancy.[19,20] By contrast, Cleary-Goldman et al. showed that IMH during the first trimester is associated with macrosomia (adjusted OR = 1.97) among 10,990 American women.[11] Evidence from van Mil et al. also indicated that IMH in the first trimester is associated with increased head sizes (β = 1.38) among fetuses and infants of 4,894 Dutch women.[34] In Spain, León et al. showed that IMH before 13 weeks of gestation contributes to higher birthweight (β = 109) among 2,644 participants.[12] In China, Zhu et al. and Gong et al. observed an increased risk of LGA (adjusted OR = 2.08) and macrosomia (adjusted OR = 1.94) among IMH women in the second trimester (rather than the first trimester), identified from 2,999 participants in Anhui and 3,398 participants in Liaoning,

respectively.[13,14] Additionally, Liu et al., Du et al., and Li et al. also found that first-trimester IMH, identified from studies involving 34,930 participants in Shanghai, 1,236 participants in Beijing, and 7,051 participants in Guangdong, is independently associated with an increased risk of macrosomia (with ORs of 2.48 and 3.89, respectively) and LGA (adjusted OR = 1.27).[15-17] Our hospital-based observational study demonstrated that IMH during late pregnancy is associated with both higher birthweight (β = 53) and an increased risk of LGA (adjusted OR = 1.32) compared with those in the context of euthyroidism among 11,478 consecutive participants in Jiangsu, China. This finding is in agreement with the prior reports and recent meta-analyses.[10,35,36] However, Casey et al. in the USA, Hamm et al. in Canada, and Ong et al. in Australia reported that IMH during early pregnancy has no adverse impact on fetal growth (SGA) and pregnancy outcomes among 17,298 participants, 879 participants, and 2,411 participants, respectively.[21-23] Furthermore, four studies conducted in China have revealed no significant correlation between IMH occurring either during the first and second trimesters or in the third trimester and adverse fetal growth outcomes such as LBW or SGA, macrosomia, or LGA.[24-27] At present, existing studies that examine the association between IMH and fetal growth outcomes may not yield consistent conclusions.[37] This discrepancy may be attributed to differences in study design (prospective vs. retrospective), study location (as an indicator for race/ethnicity and iodine status), sample size (ranging from hundreds to tens of thousands), cut-off values (FT4 < 2.5th percentile vs. FT4 < 5th percentile vs. FT4 < 10th percentile) and gestational age (first trimester vs. second trimester vs. third trimester) for identifying IMH, maternal TPO-Ab status, and the control for potential confounders including maternal age, BMI, gestational weight gain (GWG), pregnancy complications, and iodine status.[37] In addition, maternal TSH reference intervals vary across different ethnic populations during pregnancy, with over 90% of post-2005 studies reporting upper limits exceeding fixed cut-offs by 0.13–2.17 mU/L.[31] The 2017 guidelines of the American Thyroid Association (ATA) recommend using pregnancy-specific, population-based reference ranges or, if unavailable, an adjusted upper limit (4 mIU/L).[38] In our study, the group with obesity exhibited significantly higher mean TSH levels (3.9 mIU/L), approaching the ATA-recommended threshold (4 mIU/L), and lower mean FT4 levels, which may contribute to elevated IMH prevalence and subsequent LGA risk in this population.

Obesity has emerged as a global epidemic, with its prevalence rising dramatically worldwide. Prior research indicates that elevated BMI may serve as a proxy for IMH in pregnancy, and individuals with high BMI during early pregnancy demonstrate an increased risk of developing IMH.[39-42] The current study further revealed that the incidence of IMH among individuals with overweight or obesity during late pregnancy was significantly higher compared to those with normal weight (0.9% in normal weight vs. 4.8% in overweight vs. 8.1% in obesity), with relative risks increasing by 4.63-fold and 6.96-fold, respectively. Additionally, our findings suggest that maternal obesity is associated with reduced serum FT4 levels (β = -1.20) and elevated serum FT3 levels (β = 0.21).

This phenomenon may be explained by the adaptive response of obesity stimulating peripheral deiodinase activity to enhance energy expenditure, thereby promoting the conversion of FT4 to FT3.[43] Furthermore, studies by Li et al. and Liu et al. demonstrate that prepregnancy overweight or obesity is not only more prevalent among individuals with IMH but also independently associated with IMH development during pregnancy.[17,44] A large-scale prospective cohort study of 34,930 pregnant women in China revealed a significant synergistic interaction between prepregnancy overweight/ obesity and first-trimester IMH regarding macrosomia risk (adjusted OR = 1.65 for prepregnancy overweight/obesity; adjusted OR = 2.48 for IMH; adjusted OR = 5.26 for coexisting IMH and prepregnancy overweight/obesity).[15] The present study provides further evidence that prenatal overweight/obesity, when coexisting with third-trimester IMH, may synergistically elevate the risk of LGA infants. Specifically, the adjusted ORs were 5.88 for prenatal overweight/obesity, 1.32 for third-trimester IMH, and 7.60 when both conditions were present. Based on the aforementioned findings and our results, we propose a hypothesis that that both pre-pregnancy BMI and prenatal BMI (shaped by GWG) interact with IMH at various gestational stages, thereby multiplicatively increasing the risk of LGA newborns. The identification of stage-specific synergistic interactions between maternal obesity (prepregnancy or prenatal) and IMH carries profound clinical implications for antenatal care: (1) stratified risk screening and prevention; (2) intervention timing and modalities; (3) multidisciplinary care models; (4) patient education; and (5) policy and guideline revisions. By adopting a time-sensitive, stratified care approach that includes early thyroid optimization for pre-pregnancy obesity and late metabolic surveillance for prenatal obesity, clinicians can disrupt the multiplicative risk pathways.

The direct mechanisms by which IMH and prenatal obesity may potentially impact LGA, as well as the combined additive effect of these two unfavorable conditions on LGA, remain elusive. However, these mechanisms might serve as plausible explanations. On the one hand, thyroid hormones are essential for maintaining the delicate balance between the catabolic breakdown and anabolic synthesis of glucose, fat, and protein, and they also have the potential to directly modulate insulin secretion and its sensitivity, thereby significantly affecting overall metabolic processes.[45] Lower FT4 levels, the primary manifestation of IMH, may be linked to higher circulating glucose concentrations, leading to an increased glucose transfer from the placenta to the fetus and thereby contributing to fetal weight gain through continuous nutrient accumulation.[46] On the other hand, previous study has show that elevated maternal BMI may promote placental growth and result in an expanded placental surface, facilitating greater nutrient transfer.[47] Maternal overweight or obesity could contribute to increased levels of glucose, fatty acids, andamino acids in pregnancy, enabling them to be passed across the placenta to the fetus on a more regular basis.[48,49] These phenomena may lead to excessive fetal nutrition and elevated synthesis of insulin and insulin-like growth factors, together with insulin resistance and GDM, thereby enhancing the possibility of fetal overgrowth.[50] In general, both IMH and prenatal obesity in pregnant individuals might affect the risk of LGA by altering the intrauterine nutritional environment through the regulation of growth-promoting hormone levels, their sensitivity, and fetal nutrient uptake.[15] Moreover, prenatal obesity has the potential to predispose individuals to IMH, ultimately leading to a cumulative impact on the risk of LGA. Consequently, the synergistic effect of IMH and prenatal obesity on LGA is biologically reasonable.

Strengths and limitations

Our results enrich the literature concerning the adverse impact of prenatal obesity on thyroid hormone levels, which

might contribute to an increased risk for fetal impairment linked to IMH and LGA. This retrospective analysis of a vast sample size drawn from real-world data empowered us to take into consideration major confounders, including maternal demographic characteristics and routine laboratory findings. Importantly, we considered maternal pregnancy complications and TPO-Ab status. Additionally, we carried out multiple sensitivity analyses and subgroup analyses in this study to guarantee the reliability of the findings. For instance, GDM, a prevalent pregnancy complication, plays a significant role in the pathogenesis of LGA infants, and women with obesity are at a higher risk of developing GDM. Although subgroup and sensitivity analyses were conducted among women without pregnancy complications, the potential influence of GDM cannot be overlooked when evaluating the combined effects of obesity and IMH on LGA. Finally, to the best of our knowledge, this is the first study to focus on antenatal obesity and IMH, with interaction, on the risk of LGA deliveries in Chinese women. However, the following limitations should be mentioned: First, given the retrospective and observational nature of this study, we are unable to definitively establish the precise causal relationship. Second, as is the case with all retrospective observational studies, despite adjustments made for known potential confounders, such as maternal factors and laboratory results, the possibility of unadjusted or unmeasured confounders (e.g., pregestational BMI and GWG) remains. For example, our study lacked data on iodine concentrations and thyroid medication during pregnancy, which could potentially impact our results. Notably, Changzhou is an iodine-sufficient area, and Chinese pregnant women generally maintain adequate iodine intake due to the implementation of a salt iodization program since 1996.[51] Third, in this study, thyroid hormone levels were measured only once late in pregnancy, whereas the regulation of fetal growth occurs throughout the entire gestation period. Finally, this single-institution, retrospective analysis uncovers an association within the Chinese population, but its generalizability to other centers and populations remains to be confirmed.

Conclusion

In a cohort of Chinese pregnant women from a large tertiary hospital, we observed that the subgroup with obesity and IMH in late pregnancy demonstrated an elevated likelihood of delivering LGA newborns. If validated, these findings may have important public health and clinical relevance, particularly given the growing global focus on LGA-related health outcomes. Our results suggest that integrating BMI evaluation with thyroid hormone profiling may assist in identifying individuals at higher risk of LGA deliveries.

Abbreviations

IMH	Isolate maternal hypothyroxinaemia
SGA/AGA/LGA	Small/appropriate/large for gestational age
BMI	Body mass index
BP	Blood pressure
GDM	Gestational diabetes mellitus
ICP	Intrahepatic cholestasis of pregnancy
PE	Preeclampsia
PIH	Pregnancy-induced hypertension
PTB	Preterm birth
FT3	Free triiodothyronine
FT4	Free thyroxine
TSH	Thyroid stimulating hormone
TPO-Ab	Thyroid peroxidase antibody
RBC	Red blood cells
WBC	White blood cells
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval
OR	Odds ratio

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Author contributions

BZ and XY conceived and designed this study. X Y wrote the manuscript. SX collected the data. ZZ and YZ analyzed and interpreted data. All authors reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Ethical Committee of Changzhou Maternal and Child Health Care Hospital (ZD201803). Due to anonymous data recorded in the present study, the requirements for written informed consent were waived by the Ethical Committee of Changzhou Maternal and Child Health Care Hospital. All methods in this study were carried out in accordance with relevant guidelines and regulations.

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Ten-Year Review of Hospital-Acquired Neonatal Meningitis in a Tertiary-Level NICU: The Important Role of Acinetobacter Species

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Abstract

Background

Meningitis during the neonatal period is a potentially devastating condition with high morbidity and mortality. Pathogens cause meningitis varying with gestational age at birth, age at presentation, and geographic location.

Methods

This 10-year retrospective cross-sectional study, conducted from 2014 to 2023, involved thoroughly evaluating patient files who developed hospital-acquired neonatal meningitis during their hospitalization, with the aim of identifying the causative pathogens and predisposing factors to mortality and hydrocephalus. in a large, referral neonatal intensive care unit at Imam Khomeini Hospital in Ahvaz, Iran.

Results

The files of 33 infants with meningitis were examined. The number of premature and low birth weight babies was 30(90.9%) and 27(81.8%), respectively. The studied neonates' mean gestational age and birth weight were 32.6 ± 3.3 weeks and 1812 ± 739 g, respectively. Meningitis with late-onset occurred in 28(84.8%) infants and Gram-negative bacteria in 24(72.7%) infants. Out of a total of 33 neonates with meningitis, 13(39.3%) of whom died. The pathogen most frequently isolated from cerebrospinal fluid cultures was Acinetobacter species, found in 16(48.4%) patients. Occurrences of seizures in the first three days of meningitis, meningitis with gram-negative bacteria, and leukocytosis of more than 15,000 at the onset of meningitis increased the probability of death and hydrocephalus in infants.

Conclusion

Considering that most of the neonates in this study were premature, had low birth weight, and had nosocomial late-onset meningitis with Gram-negative bacteria, it is necessary to prevent them from contracting meningitis with strict and multifaceted care while hospitalized.

Introduction

Bacterial meningitis in infancy is still one of the most debilitating diseases. In developed countries, the frequency of proven meningitis by positive cerebrospinal fluid culture is 0.3% per 1000 live births, and in developing countries, this rate is 0.8 to 1.6. The mortality rate in developed countries is 10-15%. In developing countries, this percentage is up to 58%. Additionally, severe complications affect 20 to 60% of infants.[1,2] The risk factors for meningitis in a newborn include prematurity, low birth weight, male gender, asphyxia, multiple pregnancies, chorioamnionitis in the mother, and grade 3 and higher intraventricular hemorrhage in the newborn.[3,4] Neonatal meningitis is divided into two general categories: 1- Early-onset (first 7 days of life) and 2- Late-onset (8 to 28 days of age).[5] Late-onset meningitis often occurs in premature neonates and nosocomial form. The pathogens that cause meningitis are similar to those that cause sepsis. Based on the neonate's gestational age, postnatal age, hospital conditions, and geographical location, the bacteria causing meningitis changes over time.[5] *Group B Streptococcus (GBS)* is still the most common cause of sepsis and meningitis in developed countries, as this pathogen is responsible for more than 40% of early-onset infections.[4] The next pathogen in terms of prevalence is *Escherichia coli* (*E. coli*), which is the most common cause of sepsis and meningitis in very low birth weight neonates. In late-onset meningitis, the most common organisms are coagulase-negative staph and staph aureus, after which *E. coli and Klebsiella* are the causative agents of meningitis.[6] In developing countries, most bacteria causing meningitis are Gram-negative, such as *Klebsiella*, *Acinetobacter*, *E. coli*, *Pseudomonas*, *Enterobacter*, and *Serratia*. From the group of gram-positive bacteria, in addition to coagulase-negative staph and staph aureus, enterococci also commonly cause meningitis.[7] Boskabadi et al., in a study they conducted in Iran, mentioned most common pathogens causing meningitis were *Klebsiella pneumoniae* and *Entrobacter aerugenes*, and the mortality rate due to meningitis in this study was 36%.[8] Amber Azim and colleagues, in a study that examined the etiological factors of neonatal meningitis in India, reported that the most common causative pathogen was *Acinetobacter spp* (42%) and higher mortality due to meningitis (35-16%) in early-onset compared to late-

onset.[9] Musa Mohammed Ali from Ethiopia mentioned *Acinetobacter species* as the second most common cause of neonatal meningitis (13.3%) after *coagulase-negative staph* (28.9%). On the other hand, *Acinetobacter species* are reported as the most common cause of late-onset meningitis with Gram-negative bacteria.[10] Samia Aleem and colleagues, in a 5-year multicenter study in the United States, reported a mortality rate of 9% due to neonatal meningitis.[11] Considering the change of the etiological factors causing meningitis over time and place, the high rate of death and numerous and severe complications of this disease, as well as the previous study that was conducted in our province in this field,[12] this study aims to identify possible changes in pathogens and predisposing factors to death, to review the files of patients who were diagnosed with bacterial meningitis and treated for 10 years (from 2014 to 2023) in the neonatal special care department of Imam Khomeini Hospital in Ahvaz, Iran. This study's results can help correctly use antibiotics and plan to reduce mortality and complications caused by this disease.

Methods

This retrospective cross-sectional study examined the records of infants admitted to the Neonatal Intensive Care Unit of Imam Khomeini Hospital in Ahvaz with meningitis in 10 years (from 2014 to 2023). The files of patients with clinical signs of meningitis in the first four weeks of life (poor feeding, respiratory distress, lethargy, irritability, convulsions, tremors or staring, hypotonia, or hypertonia, and fever) and positive CSF culture were examined. To confirm neonatal meningitis based on CSF culture, a cerebro spinal fluid white blood cell count of more than 21 cells/mm3 indicates a sensitivity of 97% and specificity of 81%.[13,14] Neonates with major congenital anomalies, clinical symptoms consistent with chromosomal disorders, and meningitis after 28 days of age were excluded from the study. The information extracted from the mother's and neonate's records includes the age of the mother, pregnancy rank, history of PROM more than 18 h, urinary tract infection(UTI), fever, receiving corticosteroid, chorioamnionitis, antibiotic therapy before delivery and mode of delivery, gestational age of the neonate, gender, birth weight, primary cause of hospitalization, history of respiratory distress and receiving oxygen through NCPAP or the ventilator, mentioning its duration, the age of the infant when he contracted meningitis, hospital stay, and the infant outcome (alive/dead). Also, the leukocyte and platelet count, blood culture results, cell-biochemical analysis of CSF, and the type of organism isolated from CSF culture were extracted from the patient's files. In terms of gestational age and birth weight, the studied neonates are divided into two groups: term (37 weeks of pregnancy or more), preterm (less than 37 weeks of pregnancy), normal weight (equal to or more than 2500 g), low weight (less than 2500 g).) were divided. Regarding the onset of meningitis, the patients were divided into early-onset meningitis (first week of life) and late-onset meningitis (from 8 to 28 days) of age. The patients were categorized into two groups: those who survived and those who died.

Table 1 Clinical characteristics of mothers and infants with meningitis

Variables	Number	Percent
Perinatal information		
Urinary tract infection	2	6%
Premature rupture of membrane	13	39.3%
Intrapartun antibiotic therapy	14	42.2%
Neonatal information		
Gestational Age		
32weeks≤	19	57.5%
32weeks >	14	42.5%
Birth Weight		
1500 g≤	19	57.5%
1500 g >	14	42.5%
Sex		
Male	14	42.4%
Female	19	57.6%
Delivery Method		
C/S	21	63.6%
V/D	12	36.4%
Type Of Meningitis		
Early-onset	5	15.2%
Late-onset	28	84.8%
Outcome		
Alive	20	42.4%
Dead	13	39.3%
Clinical information		
Apnea	23	69.6%
Poor feeding	21	63.6%
Hypotension	11	33.3%
Seizure	11	33.3%
Fever	6	18.1%

Antimicrobial susceptibility testing was done using the standard Kirby Bauer disk diffusion method on Muller Hinton agar (MHA) plates as per Clinical and Laboratory Standard Institute (CLSI) guidelines. 2022, M100.[15] Ethics approval and consent to participate: The approval and code of ethics (IR.AJUMS.HGOLESTAN. REC.1403.071) were issued by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences. In the statistical analysis of quantitative variables, the mean or median is used to describe the center of the data, while the standard deviation or interquartile range is used to describe the dispersion of the data. For qualitative variables, frequency and percentage are used to describe the data. Univariate data analysis uses independent t-tests or Mann-Whitney tests for quantitative variables and Chi-square tests or Fisher's exact tests for qualitative variables. All independent variables between the two groups are compared to identify risk factors for mortality. Any variables with a p-value less than 0.05 are considered significant. All analyses are performed using SPSS software version 25.

Results

During the study period, 33 infants were diagnosed with meningitis through clinical manifestations and positive CSF cultures. Concerning prenatal risk factors, The frequency of premature rupture of membranes (PROM), Urinary tract infection(UTI), and fever in mothers of newborns with meningitis were 13 (39.3%), 2 (6%) and 1 (3%) cases, respectively. Of the studied infants, 30(90.9%) were premature, 27(81.8%) had low birth weight, and 14(42.4%) were male. The infants' mean gestational age and birth weight were 32.6 ± 3.3 weeks and 1812 ± 739 g, respectively. Twenty-one (63.3%) of the neonates were delivered by cesarean section. The mean age at onset of meningitis and the period of hospitalization were 12.6 ± 5.7 and 37.2 ± 20.5 days, respectively. Late-onset

Table 2 The prevalence of bacteria related to different types of meningitis and infant outcomes

Bacteria	Type of meningitis		Outcome		Total
	Eariy-onset	Late-onset	Alive	Dead	
	N(%)	*N*(%)	*N*(%)	*N*(%)	
Acinetobactor spp.	3(18.8%)	13(81.3%)	7(43.8%)	9(56.2%)	16
Staphylococcus aureus	0(0.0%)	8(100%)	7(87.5%)	1(12.5%)	8
Klebsiella pneumaniae	0(0.0%)	5(100%)	2(40%)	3(60%)	5
Escherichia coli	0(0.0%)	2(100%)	2(100%)	0(0.0%)	2
Pseudomonas aeruginosa	1(100%)	0(0.0%)	1(100%)	0.0%1))0	1
Enterococcus	1(100%)	0(0.0%)	1(100%)	0(0.0%)	1
Total	5	28	20	13	33

meningitis was observed in 28 (84.8%) of the neonates. The blood culture positivity rate was 10 (30.3%%) in neonates. The number of deceased infants was 13 (39.3%). Gram-negative pathogens were isolated from CSF cultures in 24 cases (72.7%), with Acinetobacter species being the most common pathogen, isolated in 16 cases (48.4%). Methicillin-resistant Staphylococcus aureus was isolated from cerebrospinal fluid cultures of 8 (24.2%) infants as the most common gram-positive pathogen causing meningitis. The mean leukocyte count., protein, and glucose levels in CSF examination were 2445 ± 386, 129 ± 88, and 41 ± 26 mg/dl, respectively. The most common clinical sign at the onset of meningitis was apnea, which occurred in 23 (69.7%) infants. Seizures occurred in 11 (33.3%) neonates in the first three days of the onset of meningitis. (Table 1).

In the assessment of antibiotic resistance in Gram-negative bacteria isolated from cerebrospinal fluid, it was found that the resistance rates to ampicillin and cefazolin were 100%. The resistance to third-generation cephalosporins ranged from 78 to 100%. For aminoglycosides, the resistance rates to gentamicin and amikacin were 58% and 50%, respectively. The resistance to meropenem was 56%. All gram-positive bacteria were resistant to Ampicillin, Cefazolin, and Methicillin but sensitive to clindamycin and vancomycin at 100% and 87.5%, respectively. All cases of meningitis caused by *Staphylococcus aureus* and *Klebsiella pneumoniae* were of the late-onset type. *Staphylococcus aureus* had the lowest mortality rate, while *Klebsiella pneumoniae* had the highest (Table 2).

There was no significant relationship between the delivery method, gestational age, birth weight, sex of the neonates, and type of meningitis with the mortality and morbidity(hydrocephaly) of infants ($P > 0.05$). However, Seizure, peripheral leukocytosis (more than15000 /µL), and type of bacteria were significantly related to the mortality and morbidity of infants with meningitis ($P < 0.05$). In the logistic regression model, it was found that seizure in the first three days of the onset of meningitis and meningitis with gram-negative bacteria increases the probability of death and hydrocephaly with an odds ratio (OR) of 14.44, CI 95% (1.56–133.58, $p = 0.009$), and 8.50, CI 95% (1.40–51.48, $p = 0.020$) compared to neonates without seizure and meningitis with gram-positive bacteria (Table 3).

Discussion

Our study, which investigated prenatal factors contributing to neonatal meningitis, revealed that 39.3% of mothers had a history of prolonged rupture of membranes (PROM), a higher percentage than the 19% reported by Boskabadi H et al. for mothers of infants with meningitis.[8] Mulugeta Nigusu Wondimu et al. from Ethiopia highlighted that prolonged rupture of membranes causes a 5.38-fold increase in neonatal meningitis.[16] Based on the results of a systematic review, one of the main factors in the occurrence of PROM is infection (mostly bacterial infection) that stimulates the release of pro-inflammatory cytokines from decidua and amniotic membranes. Therefore, many bioactive materials, such as prostaglandins and metalloprotease, are released. So prostaglandins stimulate uterine contractions, and metalloprotease causes cervical softness and, eventually, membrane tearing.[17] Maternal infection leading to premature rupture of the membrane may be transmitted to the fetus via the placenta or vaginal canal and result in sepsis and neonatal meningitis. The results of one study showed that the risk factors for prenatal neonatal meningitis include PROM, maternal vaginitis, and asymptomatic bacteriuria.[3]

Our study revealed that late-onset meningitis occurs significantly more often than early-onset meningitis (84.8% v/s 15.2%). This finding is consistent with the seven-year retrospective study conducted by Biset S and colleagues, which stated that the frequency of late-onset meningitis in cases of positive CSF culture is 89.4%.[18]

The infants in this study were primarily premature, low birth weight, had been hospitalized in the ward from the first minutes after birth, and had received antibiotics upon admission. These characteristics increase the risk of nosocomial infections, making it unlikely for meningitis to develop within the first three days of life in this population. Therefore, this study classified the onset of neonatal meningitis based on the first seven days of life and thereafter.

It is important to note that as newborns' hospitalization length increases, there is a greater need for frequent examinations, diagnostic-therapeutic (invasive and non-invasive) measures, and changes in antibiotics. This combination of factors increases the risk of late-onset meningitis in neonates.

Pathogen distribution and comparison with other studies

In our investigation of the causes of meningitis, we found Gram-negative pathogens occur much more frequently than Gram-positive ones (72.7% vs. 27.3%), a finding that aligns with research from Sirak Biset in Ethiopia, Qian Zhai in China, and Mashau RC in South Africa.[18-20] However, it is essential to note that this trend may only apply to some countries. For example, a nationwide study by Oncel MY et al. in Turkey reported a higher frequency of Gram-positive pathogens (54.5%),[21] contrasting our findings. Our study identified Acinetobacter species as the most common pathogen isolated from cerebrospinal fluid cultures (48.4%). This finding is consistent with the findings of Azim et al. from India (42%), Mashau RC from South Africa (23%), and Anucha Thatrimontrichai et al. from Thailand (32%), demonstrating the widespread prevalence of *Acinetobacter species* in meningitis.[9,20,22] This consistent prevalence across different regions and populations from Asia and Africa highlights the significance of our findings; contrary to this finding, the United States of America, in China, and European countries,

Table 3 A logistic regression analysis examining the relationship between variables and the occurrence of hydrocephalus and mortality

Variables	Heatly (14)	Mortality/morbidity(19)	OR 95%(CI)	*P*.value
Prolonged PROM				
No	7	13	1	0.288
Yes	7	6	0.462 (0.111–1.921)	
IPA				
No	7	12	1	0.451
Yes	7	7	0.583 (0.144–2.371)	
Mode of delivery				
C/S	9	12	1	0.999<
V/D	5	7	0.962 (0.228-4.00)	
Gestational Age (weeks)				
32 or more	8	11	1	0.966
Less than 32	6	8	1.031 (0.255–4.167)	
Birth weight (grams)				
1500 or more	12	7	1	0.451
1500 than Less	7	7	1.714 (0.422–6.968)	
Type of meningitis				
Early– onset	2	3	1	0.905
Late– onset	12	16	1.125 (0.162–7.824)	
Type of bacteria				
Gram Positive	7	2	1	0.020
Gram Negative	7	17	8.50 (1.40-51-48)	
Apnea				
No	4	6	1	0.853
Yes	10	13	0.867 (0.191–3.923)	
Poor feeding				
No	6	6	1	0.716
Yes	8	13	1.625 (0.387–6.817)	
Seizure				
No	9	13	1	0.019
Yes	1	10	14.44 (1.56-133.58)	
Platelet Count				
150,000 and more	11	14	1	0.764
Less than 150,000	3	5	1.310 (0.255–6.715)	
leukocyte count Blood				
Less than 15,000	11	7	1	0.023
15,000 and more	3	12	6.28 (1.29–30.53)	

the most common pathogen causing meningitis is *E. Coli*. whose frequency is 55%, 21.3%, and (22.2%), respectively.[11,23,24] A previous study in this center showed that *Acinetobacter species* are in the fifth rank regarding the prevalence of bacteria causing neonatal meningitis.[12] Changes in the frequency of pathogens responsible for meningitis aligns with reports from Türkiye and South Africa, where changes in pathogen profiles over time in neonatal intensive care units have also been documented.[25,26] Changes in the factors such as a decrease in gestational age and birth weight of infants, an increase in patients requiring invasive ventilation, higher use of PICC and central venous catheters, higher broad antibiotic usage, particularly carbapenems, increased intravenous nutrition use, could be related to the change in pathogens causing meningitis in our department. In a Mini Review study, Kamla Pillay et al. examined risk factors for Acinetobacter spp. Sepsis in neonates reported that intubation, prematurity, low birth weight, mechanical ventilation, central venous catheters, and previous antibiotic use were considered risk factors in most studies.[27]

Clinical and antibiotic treatment implications

We found that Gram-negative bacteria, particularly *Acinetobacter spp*, were multidrug resistant. This aligns with a study by Shah MH et al. from India,[28] prevalence of antibiotic resistance in neonates in our ward. Contrary to developed countries where there are clinical guidelines more strictly implemented to restrict antibiotic misuse, antibiotic misuse or overuse is almost universal in developing countries owning to weak national and regional clinical practice policies on antibiotic use, frequent intrapartum prescription antibiotics to pregnant women, and to neonates on admission to NICU promotes the development of antibiotic-resistant bacteria. Thus, maternal exposure to antibiotics could alter maternal and offspring's bacterial profiles and favor resistant pathogens in neonates.[29]

Acinetobacter species and other gram-negative bacteria causing neonatal meningitis are frequently multidrug-resistant and associated with high mortality rates. Therefore, revising

previous empirical treatment protocols and exploring new therapeutic combinations is essential.

In a multicenter study, Biljana Kakaraskoska Boceska and her colleagues investigated the effectiveness of combination therapy using two out of three antibiotics, fosfomycin, flomoxef, and amikacin, to treat multidrug-resistant gram-negative infections in infants. The researchers concluded that the combinations of fosfomycin with amikacin, fosfomycin with flomoxef, and flomoxef with amikacin demonstrated synergistic interactions. Both bactericidal activity and the prevention of resistance emergence evidenced this. The study suggests that in regions where neonatal infections caused by multidrug-resistant gram-negative bacteria are prevalent, empirical treatment with these combinations could be a suitable alternative to the current therapies recommended by the World Health Organization (WHO).[30]

The mortality rate in this study was 39.3%, which is close to the previous study in this center (32%)[12] and also to the study conducted in the northeast of Iran (36%).[8] Contrary to our finding, a lower mortality rate was reported in a nationwide study conducted in Turkey (23.5%),[21] far from our review in a large multicenter study conducted in the United States of America, where mortality of neonatal meningitis reported at 9%.[11] Considering that all infants with meningitis in the study ward, except one case, had hospital-acquired meningitis, and the high percent of neonates were preterm and low birth weight, the majority of pathogens causing meningitis in the study department are multi-drug-resistant gram-negative bacteria. As a result, there was no decrease in mortality compared to the previous study and higher compared to other studies in other regions of Iran and other countries.

Risk factors for mortality and hydrocephalus

In investigating mortality and morbidity (hydrocephaly) risk factors, our study determined that seizures in the first three days of the onset of meningitis and infection with gram-negative bacteria increase mortality and morbidity in infants by 14.4 and 5.8 times, respectively. Similar to our findings, Liu et al., in a systematic review study that examined predictive risk factors in neonatal meningitis, mentioned that seizures determine a poor prognosis in those with neonatal meningitis.[31] In agree with and disagree with our findings, In a 17-year study, Mei-Chen Ou-Yang and colleagues from Taiwan reported that the occurrences of seizures in infants affected by meningitis increased by 2.4 times in unfavorable outcomes compared to those who had no seizures at the onset of meningitis. On the other hand, these researchers have stated that the type of bacteria did not significantly affect the outcome of infants with meningitis.[32]

Limitations and future directions

Our study is retrospective, meaning some variables may not be recorded in the patient's files. This limitation affects the results we can obtain during analysis. Another limitation of our study is the small sample size, which may be due to its focus solely on cases of neonatal meningitis with positive cerebrospinal fluid cultures. Additionally, we did not segment the study period to compare changes in pathogens and antibiotic resistance among those causing meningitis. Prospective multicenter studies are needed to obtain more comprehensive information about hospital-acquired neonatal meningitis.

The strength of this research

The strength of this research is its long duration, the discovery of changes in the pathogens that cause meningitis, and the identification of risk factors for hydrocephaly and mortality in the studied infants.

Conclusion

This research identified a high incidence of neonatal meningitis primarily caused by *Acinetobacter* species. We also observed that the bacteria responsible for meningitis exhibit multidrug resistance. Our findings indicate that leukocytosis exceeding 15,000 white blood cells, the presence of convulsions, and the occurrence of meningitis caused by gram-negative bacteria significantly increase the risk of hydrocephalus and death. There is a need for multicenter prospective studies to examine prognostic factors in neonatal meningitis. To prevent hospital-acquired neonatal meningitis, a combination of strict infection control practices is essential. These practices include hand hygiene, sterile techniques, staff cohorting, staff training, neonatal monitoring, promoting breastfeeding, and minimizing the use of invasive devices. Additionally, to reduce the mortality rate associated with neonatal meningitis, it is crucial to implement measures such as the use of new rapid diagnostic tests, timely antibiotic therapy, appropriate dosing, antibiotic stewardship, supportive care, and multidisciplinary care.

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Author contributions

SMHA: concept and design of the study; AM: drafted the work and substantively revised it, MD: interpreted data, MRA: analyzed data, AKH: Wrote the draft of the work, and SF: Has collected information. All authors have read and approved the final version of the manuscript.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Research Office of Imam Khomeini Hospital. Ahvaz.Iran.

Ethics approval and consent to participate

The research was conducted with the approval of the Pediatrics Department and the Research Vice-Chancellor of Ahvaz University of Medical Sciences and in accordance with the World Medical Association Declaration of Helsinki.

Given that this study was retrospective, its information was extracted from patient records. Due to the lack of access to the parents of the infants studied, the Ethics Committee of

Ahvaz Jundishapur University of Medical Sciences provided a form stating that parental consent was not required. The Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences provided the code (IR.AJUMS.HGOLESTAN.REC.1403.071). to authorize the initiation of this study.

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Early Metabolic Screening Shows Long-Term Benefits, but Limitations Remain

Newborn screening for genetic metabolic diseases helps a portion of children stay healthy as they grow, but decompensation episodes still occur in the first weeks after birth before test results come back, a new study by German researchers in *Pediatrics* found. The American Academy of Pediatrics recommends all newborns undergo screening for metabolic conditions like phenylketonuria (PKU), maple syrup urine disease (MSUD), and mitochondrial trifunctional protein deficiency (MTPD) within 48 hours after birth. The study followed 257 children with an identified metabolic condition from screening in the first days following birth to a median age of 13.7 years. A little over 70% never exhibited symptoms of their disease identified through screening, but the remainder did develop permanent symptoms. Approximately 81.4% of the children had normal IQs, and over 90% attended regular schools. Other conditions included in the analysis were long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and isovaleric aciduria (IVA). Researchers also analyzed data of children with disorders other than PKU (n = 154) and found nearly 45% experienced a metabolic decompensation, defined by a hospitalization stay because of a related symptom such as hypoglycemia or acidosis, within the first 28 days of life. Nearly half of these episodes occurred even before screening results were available. "This study illustrates that while newborn screening can identify neonates at risk of metabolic disease, there are still limitations," said Amy Kritzer, MD, clinical chief of the Division of Genetics and Genomics and director of the Metabolism Clinical Program at Boston Children's Hospital in Boston. Kritzer was not involved in the study. Certain diseases were more likely to cause complications. All children (n = 38) with more severe forms of conditions like MSUD (> 90% in the first 28 days) and LCHADD/MTPD (> 80% in preschool) developed a metabolic decompensation requiring hospitalization. During a median follow-up period of 13 years, the latest metabolic decompensation was reported at a median age of 6.6 years (range, 0-19.3).

Revvity Expands Alliance with Genomics England to Drive Research

Revvity, Inc. announced an agreement with Genomics England to further collaborate on the Generation Study. Under the new contract, Revvity will now also provide DNA sequencing services to help screen newborns for rare genetic conditions. This expanded relationship builds upon the previously disclosed agreement to perform DNA extraction services. Revvity will now be able to provide an integrated end-to-end solution with a localized lab facility, which will allow for accelerated extraction and sequencing services to advance the screening process for these rare conditions. The Generation Study, a research project spearheaded by Genomics England in partnership with the National Health Service, is a landmark national initiative aimed at screening up to 100,000 newborns for more than 200 rare genetic disorders. The findings will help inform future decisions on using whole genome sequencing (WGS) in newborn screening. Proactive genomic screening could help healthcare professionals identify risks for pediatric-onset conditions sooner, enabling earlier interventions and personalized care. "It is an honor to enhance our collaboration with Genomics England as we align to expand access to genomic sequencing in England. Our complete solution and localized lab facility help us deliver timely and reliable sequencing data in support of this critical program that strengthens newborn health," stated Dr Madhuri Hegde, Revvity's senior vice president and chief scientific officer. "Revvity's expansive global laboratory network combined with our next-generation sequencing solutions and workflows for newborn screening uniquely positions us to lead this and similar initiatives, setting a standard for future programs." "This collaboration is an important step forward in our mission to generate evidence on the use of genomic sequencing in newborn screening. By working with Revvity as one of our sequencing partners for the Generation Study, we can integrate sequencing alongside extraction, streamlining the process, and generating results more efficiently, helping families get answers and access to care sooner," said Dr Ellen Thomas, chief medical officer at Genomics England.

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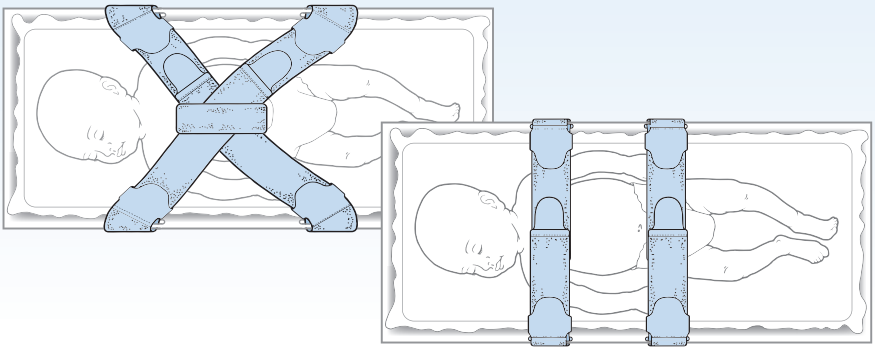

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