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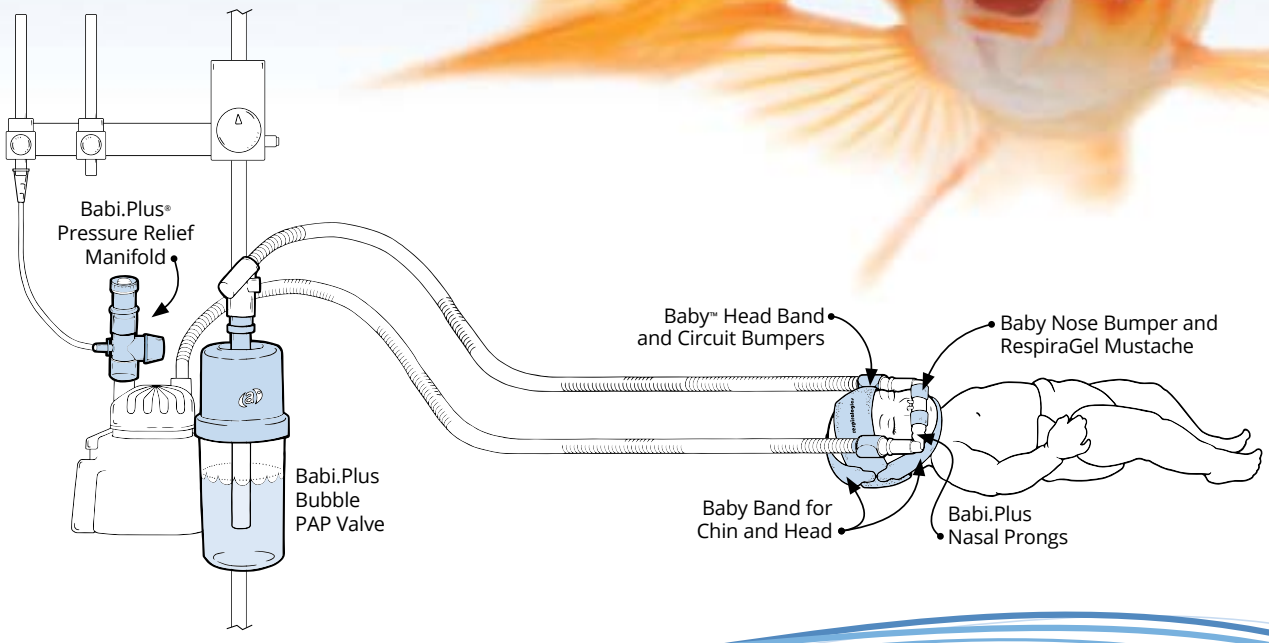

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A Review of Some Basics—Gas Laws During Mechanical Ventilation Impact on Compressible Volume Loss in Circuits

Edwin Coombs, MA, RRT, NPS, ACCS, FAARC

Recently a study was published that examined performance characteristics of high-frequency infant ventilators that may raise concerns over how measurement accuracy can be affected with respect to effective tidal volume delivery and/or impact on delivered pressure/amplitude. This brief article will review gas laws and how their respective variables can have an impact on the delivery of mechanical breaths.

The ideal gas law defines a relationship between pressure, volume, temperature, and the number of gas molecules. Pressure and volume are inversely related; whereas temperature is directly proportional to volume or pressure.[1]

Boyle's law states that at a constant temperature, pressure is inversely proportional to volume. This law predicts the relationship of a volume of gas to a pressure change.[1,2] Temperature (ie: warm ventilator tubing) also contributes to changes in tubing compliance.

Gay-Lussac's law of pressure and temperature describes the direct relationship between pressure and temperature. If the absolute temperature of a fixed volume of gas is increased, the pressure will increase proportionally.[1,2]

Charles's law predicts the effect of temperature on a fixed amount of dry gas. At a constant pressure, gas expands proportionally to changes in absolute temperature.[1,2]

The patient circuit of a mechanical ventilator conducts the breathing gas from the ventilator to the patient and from the patient to the expiratory valve of the ventilator. Tubing expansion can be seen when high pressure is generated within the patient circuit. The circuit can often be seen to expand during inspiration and then return to its original size during exhalation. Part of the inspiratory pressure or tidal volume delivered from the ventilator contributes to this tubing expansion, and as a result, it is attenuated before reaching the distal airways.

This phenomenon is extremely important when ventilating infants and children, especially when utilizing high-frequency ventilation. For this reason, a low-compliance circuit must be utilized.[2]

The use of HFOV in infants is to protect extremely premature and fragile lungs from ventilator-induced lung injury through a protective ventilation strategy. Typically, initial HFOV settings in infants are: a MAP of 2-3 cmH_2O above conventional ventilation; power to achieve an amplitude that results in visible "chest wiggle"; and a frequency of 10 Hz.[3]

While bench studies are an integral component that contributes to the advancement of science and our understanding of respiratory care products, researchers and clinicians must take into account all factors which can potentially impact how devices, accessories and related consumables deliver mechanical ventilation. Understanding research study design and methodology is critical when evaluating the results of equipment tests.

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Edwin Coombs is the Sr. Director of Marketing, Intensive Care at Dräger.

News

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New Trial Deepens Debate Over Late-Preterm Steroids

The early cancellation of a trial in southern India suggests that the use of antenatal steroids to prevent respiratory complications after late-preterm birth — a recommended practice in the United States — may not be effective in the developing world. As reported in *Obstetrics & Gynecology*, researchers led by Hilda Yenuberi, MD, of Christian Medical College, Vellore, Tamil Nadu, India, stopped the randomized, triple-blinded, placebo-controlled CLAP (Corticosteroids in Late Pregnancy) study at 70% enrollment. An interim analysis found no benefit from prescribing betamethasone vs placebo to women at risk of late-preterm delivery between 34 and 36 and 6/7 weeks of gestation (primary outcome of respiratory distress: 4.9% vs 4.8%, respectively, relative risk [RR], 1.03; 95% CI, 0.57-1.84; number needed to treat = 786). "These findings may suggest differing efficacy of antenatal corticosteroids in developing countries compared with developed countries ... that should be considered when late-preterm antenatal corticosteroids are administered," the researchers wrote. The use of steroids in patients at risk of delivery before 34 weeks is widely accepted as a way to prevent neonatal respiratory distress, a common and potentially deadly condition in premature infants whose lungs are not fully developed. However, there's debate over steroid treatment in women who are expected to deliver later than 34 weeks but still preterm. As the study notes, "the American College of Obstetricians and Gynecologists recommends a single course of betamethasone for pregnant individuals at risk of delivering between 34 and 36 6/7 weeks of gestation on the basis of the ALPS (Antenatal Late Preterm Steroid) trial." But other randomized trials have reached different conclusions, and steroids are not without risks. Studies have linked prenatal steroids to neurosensory disorders in babies, meaning they're more likely to need hearing aids and eyeglasses.

Safety Risks Persist With Out-of-Hospital Births

Safety concerns persist for out-of-hospital births in the United States with multiple potential risk factors and few safety requirements, according to a paper published in the *American Journal of Obstetrics and Gynecology*. In 2022, the Centers for Disease Control and Prevention (CDC) reported the highest number of planned home births in 30 years. The numbers rose 12% from 2020 to 2021, the latest period for which complete data are available. Home births rose from 45,646 (1.26% of births) in 2020 to 51,642 (1.41% of births). Amos Grünebaum, MD, and Frank A. Chervenak, MD, with Northwell Health, and the Department of Obstetrics and Gynecology, Lenox Hill Hospital, Zucker School of Medicine in New Hyde Park, New York, reviewed the latest safety data surrounding community births in the United States along with well-known perinatal risks and safety requirements for safe out-of-hospital births. "Most planned home births continue to have one or more risk factors that are associated with an increase in adverse pregnancy outcomes," they wrote. The researchers used the CDC birth certificate database and analyzed deliveries between 2016 and 2022 regarding the incidence of perinatal risks in community births. The risks included were prior cesarean, first baby, mother older than 35 years, twins, breech presentation, gestational age of less than 37 weeks or more than 41 weeks, newborn weight over 4,000 grams, adequacy of prenatal care, grand multiparity (5 or more prior pregnancies), and a prepregnancy body mass index of at least 35. The incidence of perinatal risks for out-of-hospital births ranged individually from 0.2% to 28.54% among birthing center births and 0.32% to 24.4% for planned home births.

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Cover: Stucco work, Thai art sculpture, Thai temple, surface. @pong Koedpoln

"The ACOG committee opinion on home births states that for every 1000 home births, 3.9 babies will die," the authors noted, or about twice the risk of hospital births. The deaths are "potentially avoidable with easy access to an operating room," they wrote.

Company Acquired in New Deal

AngelEye Health, the leading tecÚology provider for neonatal and pediatric family engagement services, announced the acquisition of NICU2Home, a company dedicated to empowering families and optimizing care coordination using tecÚology during the journey in the Neonatal Intensive Care Unit (NICU). This strategic acquisition strengthens AngelEye's commitment to holistic NICU care, expands its solutions for seamlessly connecting families with their infants, and positions the company to streamline the patient experience from admission to discharge for families and clinicians. The acquisition further positions AngelEye Health to address a critical gap in neonatal care coordination by offering numerous benefits, including: Optimized discharge coordination, planning and parent engagement. Improved communication between care teams and families. Reduction of unnecessary days in the NICU. Increased financial efficiency for hospitals. "At NICU2Home, we've dedicated more than twelve years to developing and refining our tecÚology, knowing the profound impact it can have on families navigating the complexities of the NICU journey," said Dr Craig Garfield, co-founder and co-PI at NICU2Home. "Partnering with AngelEye, a leader in the field with a vast existing network, is a game-changer. Together, we have the potential to revolutionize NICU care by empowering families and streamlining the transition home. We're excited to join forces and make this tecÚology accessible to more families across the country." AngelEye will leverage the newly combined expertise to further enhance its solutions by integrating NICU2Home with its existing family engagement platform to add a discharge management solution. The integration will provide a single consolidated experience for care teams, healthcare providers and families. The combined solution will be available to new and existing AngelEye customers in phases throughout 2024. "The acquisition of NICU2Home aligns perfectly with our mission to create a more connected and supportive NICU experience for everyone involved," said Christopher Rand, chief executive officer at AngelEye. "By integrating their innovative family engagement app with our best-in-class camera solutions and data insights, we are creating a comprehensive ecosystem that empowers families, optimizes NICU navigation and ultimately improves the transition to home." NICU2Home's user-friendly mobile app, backed by peer-reviewed research from four Chicago-area NICUs, including Northwestern Medicine, provides families with tools to stay informed and engaged throughout their NICU stay. It offers personalized educational content and insights that empower families to understand their child's condition better and to engage in the care team.

New Trial Deepens Debate Over Late-Preterm Steroids

The early cancellation of a trial in southern India suggests that the use of antenatal steroids to prevent respiratory complications after late-preterm birth — a recommended practice in the United States — may not be effective in the

developing world. Researchers led by Hilda Yenuberi, MD, of Christian Medical College, Vellore, Tamil Nadu, India, stopped the randomized, triple-blinded, placebo-controlled CLAP (Corticosteroids in Late Pregnancy) study at 70% enrollment. An interim analysis found no benefit from prescribing betamethasone vs placebo to women at risk of late-preterm delivery between 34 and 36 and 6/7 weeks of gestation (primary outcome of respiratory distress: 4.9% vs 4.8%, respectively, relative risk [RR], 1.03; 95% CI, 0.57-1.84; number needed to treat = 786). "These findings may suggest differing efficacy of antenatal corticosteroids in developing countries compared with developed countries ... that should be considered when late-preterm antenatal corticosteroids are administered," the researchers wrote. The use of steroids in patients at risk of delivery before 34 weeks is widely accepted as a way to prevent neonatal respiratory distress, a common and potentially deadly condition in premature infants whose lungs are not fully developed. However, there's debate over steroid treatment in women who are expected to deliver later than 34 weeks but still preterm. As the study notes, "the American College of Obstetricians and Gynecologists recommends a single course of betamethasone for pregnant individuals at risk of delivering between 34 and 36 6/7 weeks of gestation on the basis of the ALPS (Antenatal Late Preterm Steroid) trial." But other randomized trials have reached different conclusions, and steroids are not without risks. For the new study, conducted from 2020 to 2022 at Christian Medical College and Hospital in Vellore, India, researchers randomly assigned 423 patients to betamethasone (410 in the interim analysis; average age, 26.8 years) and 424 to placebo (415 in the interim analysis; average age, 26.2 years). The average age of participants was 26.8 years. All were between 34 and 36 6/7 weeks of gestation and expected to give birth within the next week. A quarter of participants delivered at term, which the authors wrote "may have influenced the primary outcome." The total number of neonates was 883, including 58 twin pregnancies. There was no significant difference in respiratory distress between groups, "defined as need for oxygen or continuous positive airway pressure or mechanical ventilation for at least 2 hours in the first 72 hours of life." There also were no significant differences in maternal outcomes such as chorioamnionitis or length of hospitalization or neonatal secondary outcomes such as transient tachypnea of the newborn, respiratory distress syndrome, necrotizing enterocolitis, sepsis, hyperbilirubinemia, stillbirth, and early neonatal death. Serious adverse events occurred in four neonates but none were linked to the intervention. The study doesn't discuss cost, but a 2019 report suggests that use of betamethasone to prevent neonatal respiratory distress is cost-effective. "Our findings are contradictory to those of a systematic review, the major contributor of which was the ALPS trial," the authors of the new study reported. "The primary outcome of the ALPS trial, the composite of neonatal treatment in the first 72 hours, was significantly less in the group who received betamethasone (11.6%), compared with the placebo group (14.4%; relative risk [RR], 0.80; 95% CI, 0.66-0.97)."

Infant Microbiome Development Minimally Affected by Diet, but Metabolite Profiles Differ

Diet has only a marginal impact on microbiome development in infancy, although metabolite profiles differ between breast- and formula-fed infants; circadian rhythm of the gut microbiome is detectable as early as 2 weeks after birth. A randomized, controlled interventional trial compared microbiota development in 210 newborns who were exclusively breastfed or received one of four formulas: Unsupplemented formula, *Bifidobacterium*-supplemented formula, galacto-oligosaccharide (GOS)-supplemented, or formula containing GOSs and bifidobacteria. Exclusively breastfed infants served as a reference group to evaluate the impact of infant formula feeding. Researchers tracked the infants' microbiota and metabolite profiles in response to the different feeding modes via stool samples collected periodically during the first 1-2 years of life. They also made note of the time of day that the stool sample was collected to assess 24-hour oscillations of the microbiome in relation to dietary exposure. Global microbiota assembly of infants is primarily affected by age and less so by diet. All infants showed a gradual increase in gut microbe diversity, and at 24 months, there was no observable difference between the groups. However, gut metabolite profiles differed significantly between exclusively formula-fed and exclusively breastfed infants. None of the supplemented formulas were able to fully recreate the breast milk-related microbial environment. GOS-supplemented formula was more effective at promoting sustained levels of bifidobacteria than formula containing bifidobacteria. Metabolic and bacterial profiling revealed 24-hour fluctuations and circadian networks as early as 2 weeks after birth. Infant microbes maintained circadian rhythms when grown in continuous culture, even in the absence of external light or host cues, suggesting an intrinsic clock mechanism in bacteria. "Our findings warrant the need for further analysis of circadian fluctuations of both bacteria

Continued on page 49…

A Second Case of Spondylocostal Dysplasia Including Urogenital Anomalies, Associated With Homozygous Variant c.699 G>C in Gene TBX6

Su Young Park, MD, Amrryn Halari, MBBS, Nikhitha Kotha, DO, Sameera Chaudhry, MD, Mona Khan, DO Milen Velinov, MD, Surasak Puvabanditsin, MD

Introduction

Spondylocostal Dysplasia (SCD), also known as Jarcho-Levin Syndrome (JLS), is a very rare genetic disorder characterized by vertebral and rib anomalies that result in thoracic asymmetry and pulmonary insufficiency. We present a case of a newborn diagnosed with SCD associated with Multicystic Dysplastic Kidney (MCDK). A genetic study revealed a significant TBX6 variant, c.699G>C, that is associated with the clinical findings in our patient.

SCD is a rare congenital disorder inherited in an autosomal dominant or recessive fashion. Its exact cause and prevalence are unclear. However, a few well-known genes linked to this condition have been discovered.[1] The main clinical features of these patients include a short neck, a short trunk in proportion to height, and abnormal curvature of the spine such as scoliosis or kyphosis. SCD can be suspected prenatally based on the findings of fetal ultrasound. Postnatally, radiographic studies can also reveal characteristic features of the spine and ribs, which represent segmentation abnormalities of the vertebrae throughout the spine and abnormal configuration of the ribs. Neonatal respiratory function may be compromised due to the reduced size of the thoracic cavity caused by rib abnormalities. The prognosis is directly dependent on the degree of cardiac and respiratory complications.

In addition to the multiple skeletal abnormalities, other associated anomalies include neural tube defects, hydrocephalus, Arnold-Chiari malformation, urogenital abnormalities, congenital cardiac abnormalities, extremity malformations, and hernias.[2-6] In this case report, we discuss an infant initially suspected of having SCD based on clinical-radiological findings, notably along with Multicystic Dysplastic Kidney (MCDK), who was later confirmed by genetic studies to have the homozygous TBX6 variant of SCD.

Case Presentation

This infant was born at 37 weeks and 2 days gestation via a planned primary cesarean section due to breech presentation. The mother is a 23-year-old Guatemalan immigrant having her first pregnancy who had regular prenatal care, took prenatal vitamins, and did not use alcohol, tobacco, or other drugs. Prenatal sonography revealed multiple fetal anomalies, including cystic hygroma with increased nuchal translucency, extensive vertebral malformations, bilateral foot deformities, a two-vessel cord, and increased echogenicity of both kidneys. Additionally, this pregnancy was complicated by intrauterine growth restriction, with all long bones below the fifth percentile for gestational age. The fetal echocardiogram, however, showed no cardiac abnormalities. Antenatally, Fluorescence In Situ Hybridization (FISH), karyotype, and Chromosomal Microarray (CMA) were performed, and all tests were negative for chromosomal aneuploidy or rearrangement. However, CMA demonstrated a high density of short runs (1.8 Megabase (Mb)) of allele Homozygosity (ROH) throughout the genome, consistent with a limited gene pool present in isolated populations. It also showed additional longer runs of homozygosity on chromosomes 2, 5, 11 and 16, indicative of distant consanguinity. Parents denied consanguinity. However, they were from the same small town in Guatemala.

Upon delivery, APGAR scores of 3, 7, and 8 were assigned at 1, 5, and 10 minutes of life, respectively. The infant required resuscitation efforts, including Positive Pressure Ventilation (PPV), followed by placement on Continuous Positive Airway Pressure (CPAP). He was admitted to the Neonatal Intensive Care Unit (NICU) due to respiratory distress. Despite this initial difficulty of extrauterine adaptation, the infant was successfully weaned to room air the following day.

The birth weight was 2040 grams, the length was 38 cm, and the head circumference was 32 cm. These anthropometric measurements were uniformly below the fifth percentile for age.

A physical exam was remarkable for two-vessel umbilical cord, dysmorphic facies: up-slanting palpebral fissures, arching eyebrows, and deformed low-set ears with bilateral preauricular skin tags (Figure 1). He also exhibited single palmar creases, brachydactyly of the fingers and toes, and rocker bottom feet (Figure 2). The limbs were short disproportionately to the body with otherwise normal appearance. The trunk was also relatively short with a mildly protuberant abdomen (Figure 1). A short neck with mildly limited range of motion was noted. His testes were undescended bilaterally, but the genitalia were otherwise normal. There was no evidence of any neurologic deficits. Motor responses were good, and there was full strength in both the upper and lower extremities.

Drs Park, Halari, Chaudhry, Khan, Velinov, and Puvabanditsin are with the Department of Pediatrics, Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey. Dr Kotha is with the University of New England College of Osteopathic Medicine, Biddeford, Maine.



Figure 1. (A) Note facial dysmorphism including upslanting palpebral fissures, and arching eyebrows. (B and C) Note deformed low-set ears with bilateral preauricular skin tags.

The chest cavity appeared small and asymmetric, and on palpation, the ribs were felt to be malformed and misaligned. Radiographs of the chest and abdomen were obtained. The rib cage was asymmetric, with multiple ribs being either fused, bifid, or missing bilaterally. The infant was noted to have abnormal segmentation throughout the entire vertebral column, with smooth outlines of the vertebral bodies (Figure 3). Postnatal renal and bladder ultrasound revealed bilateral renal enlargement and loss of cortico-medullary demarcation secondary to multiple cortical cysts (Figure 4). A follow-up Fluoroscopic Voiding Cystourethrogram (VCUG) showed no evidence of reflux. The renal function was normal. Postnatal Echocardiogram (ECHO) did not reveal cardiac defects except trivial Patent Ductus Arteriosus (PDA).

Although the infant had extensive diffuse vertebral abnormalities, fused and misaligned ribs, short stature with disproportionately short limbs, and brachydactyly, he did not have any neurological deficits. Therefore, the diagnosis of SCD was suspected based on a detailed history and clinical-radiological findings. A skeletal dysplasia panel (Invitae Laboratories) was sent based on the presumed diagnosis, and the patient was found to have a homozygous variant of uncertain significance in TBX6, c.699G>C.

Despite the quick resolution of respiratory distress, the infant remained in the NICU for a month, with subsequent transfer to a long-term care rehab facility due to prolonged feeding difficulties. He had a persistently weak suck, was tiring easily, and showed poor feeding cues. The patient did not reach his birth weight until he was seventeen days old. Initially, the infant had poor feeding by mouth and received most of his feeds by nasogastric tub, though by the time of transfer, he demonstrated improved feeding cues and had reached about forty percent intake by mouth.

Figure 2. (A) Note a single palmar crease and brachydactyly of the fingers. (B and C) Note deformed lower extremities with short and broad toes and congenital vertical talus (rocker-bottom appearance).


Discussion

SCD, also known as Jarcho-Levin Syndrome (JLS), is characterized by abnormalities in the spine with malformed vertebrae and an abnormal configuration of the ribs in a random pattern, leading invariably to a short trunk. These findings are either isolated or associated with other congenital anomalies. Previously reported associations include neural tube defects, hydrocephalus, Arnold–Chiari malformations, urogenital abnormalities, congenital cardiac abnormalities, extremity malformations, and hernias.[2-6] SCD can be inherited in an autosomal dominant or recessive manner. As it is a rare genetic disorder, its exact prevalence is unknown.[7] SCD has been widely misunderstood in the medical literature due to its similarity to a related disorder known as, Spondylothoracic

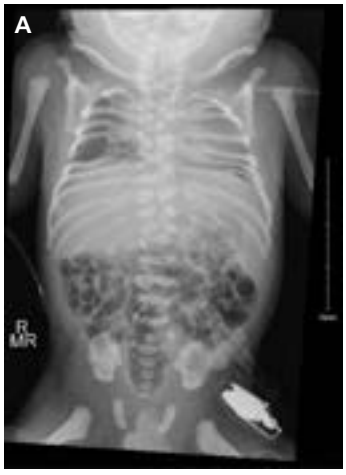
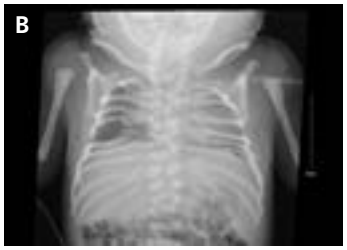

Figure 3. (A and B) Spinal radiographs show abnormal segmentation throughout the entire vertebral column, with smooth outlines of the vertebral bodies and extensive diffuse rib abnormalities.

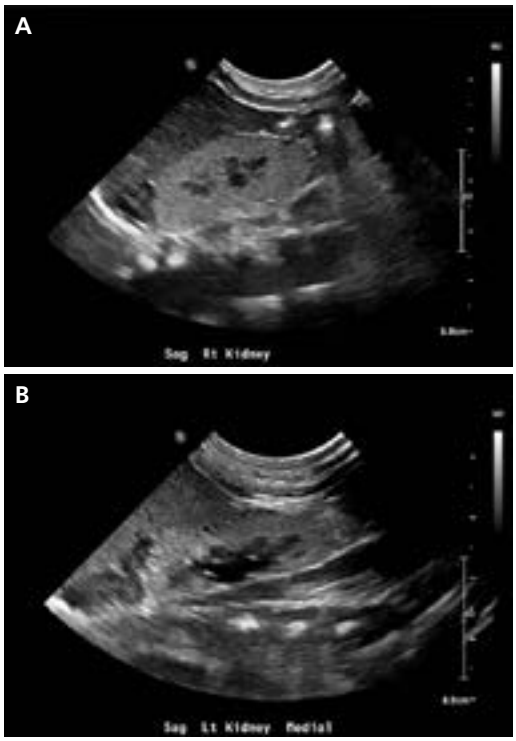

Figure 4. (A and B) (A) shows sagittal view of right kidney. (B) shows sagittal view of left kidney. Note diffusely increased renal parenchymal echogenicity with decreased cortical medullary differentiation and multiple small cysts in the cortex.

Dysplasia (STD). For many years, SCD and STD, were grouped under the "umbrella" term of Jarcho-Levin Syndrome (JLS) referring to a spectrum of conditions involving spinal and rib defects. However, these two groups of disorders are separate entities with different etiologies and distinguishable associated malformations. The prominent features of STD are vertebral segmentation anomalies with minimal intrinsic rib anomalies. The ribs are often shortened with a fusion of the ribs posteriorly at the costovertebral junctions. In contrast, SCD is distinguished by vertebral anomalies and crowding of ribs anteriorly, either due to absence or abnormal alignment, fusion, or bifurcation. The mortality of STD patients is around 50%. Surviving patients may live a healthy and independent life. SCD patients have a better prognosis with a higher proportion of survivals.[8,9]

We have previously reported a patient with SCD and kidney malformations who was also homozygous for the variant c.699G>C in gene TBX6.[12] This report further confirms the association between homozygosity for the TBX6 variant c.699G>C resulting in SCD with urogenital anomalies.

At least six different genes—DLL3, HES7, LFNG, MESP2, RIPPLY2, or TBX6—were previously associated with autosomal recessive forms of SCD. Heterozygous mutations associated with autosomal dominant inheritance were also reported for the gene TBX6.[1] Among six genes, the most common is the DLL3 gene mapped to the 19q13.1-q13.3 region.[8,10,11] Many patients do not have a mutation in any of these genes, implying that an underlying cause has yet to be discovered and will be revealed by future genetic studies.

In our case, bilateral renal enlargement and loss of cortico-medullary demarcation secondary to multiple cortical cysts were observed in renal ultrasound. It is noteworthy to mention that nonspecific and unusual involvement, like genitourinary abnormalities found in our case, was only noted in the case previously reported by us.[12] Such additional features seem to be specifically associated with homozygous TBX6 variants c.699G>C. This variant has been observed in individuals with clinical features of TBX6-related conditions when in combination with a pathogenic variant in trans. Experimental studies are conflicting or provide insufficient evidence to determine the effect of this variant on TBX6 function.[13,14] TBX6 gene is known as T-box 6, a member of the T-box family, and encodes a transcription factor which is essential for somite development and regulation during embryonic development (somitogenesis). Advanced modeling of protein structure and biophysical properties indicate that this variant is not expected to disrupt the TBX6 protein function.[14] However, our patient's features are very consistent with SCD. Based on the information available, the TBX6 variant c.699G>C in our patient is most likely linked to his manifestations.

Overall, the prognosis of severe forms of SCD is poor, but not consistently lethal. High suspicion of index in diagnosis prenatally or postnatally followed by aggressive neonatal management and care is the fundamental keystone of a better prognosis in these patients since the prognosis is directly related to cardiorespiratory complications. Therefore, for the better survival of SCD patients, preventative methods should be anticipated for pulmonary complications (such as recurrent pneumonia), congestive heart failure, and pulmonary hypertension.[15]

In summary, SCD is a rare disorder characterized by rib and vertebral abnormalities that can lead to significant respiratory compromise along the life course. Prenatally, the case was suspected using nuchal translucency screening, anatomy scanning in the second trimester, and/or three-dimensional ultrasound. Prenatal ultrasound diagnosis tecÚiques improved the high index of suspicion of diagnosis at birth, and expectant care in infancy and medical and surgical correction of thoracic insufficiency are all expected to improve these individuals' prognosis.

Acknowledgments

The manuscript and its content have been approved by all co-authors.

Contributors' Statement

Dr Park was involved in the clinical care of the patient, coordinated, and supervised the clinical data collection, critically reviewed, drafted the initial manuscript, revised the manuscript, and approved the final manuscript as submitted.

Drs Halari and Kotha conducted clinical data collection, interviewed with patient's legal guardian, obtained the informed consent for publication, and contributed to draft the initial manuscript.

Dr Chaudhry and Khan were involved in the clinical care of the patient and researched relevant references for the manuscript.

Drs Velinov and Puvabanditsin were involved in the clinical care of the patient and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest

Drs Park, Halari, Kotha, Chaudhry, Khan, Velinov, and Puvabanditsin have no conflicts of interest relevant to this article to disclose.

Financial Disclosure Statement

Drs Park, Halari, Kotha, Chaudhry, Khan, Velinov, and Puvabanditsin have nothing to disclose.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Consent Statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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Signal Processing in Nellcor™ Pulse Oximetry With OxiMax™ Technology

Clark R Baker, BS and Scott McGonigle, MEng

Background

Pulse oximetry has evolved from the standard of care in operating rooms to use across the continuum of care, including pre-hospital EMS, emergency department, critical care, post-anesthesia care and Med-Surg units.[1] Today pulse oximetry is considered the fifth vital sign, trusted by clinicians to help protect patient safety.

Pulse oximetry measures blood oxygenation noninvasively by estimating the fraction of hemoglobin bound to oxygen in pulsing arterial blood. This parameter reflects oxygen transfer from the lungs to tissues through the blood, providing an early indication of oxygenation issues in a quantitative, timely, continuous, and convenient manner.

Despite its outward appearance as a simple medical device, the pulse oximetry system is a robust clinical tool equipped with sensors, cables, electronics, signal processing, alarms, and a user interface that provides caregivers critical information for patient care (Figure 1).

This Tech Brief describes how Nellcor™ pulse oximetry distinguishes itself from alternative pulse oximeters through the technology and tools it offers patients and healthcare professionals. The history of Nellcor™ pulse oximetry technology is shown in Figure 2.

Nellcor™ pulse oximetry with OxiMax™ technology signal processing basics

Nellcor™ pulse oximetry with OxiMax™ technology signal processing is based on a physiologic tenet that has not changed since the earliest Nellcor™ pulse oximeter was introduced — a patient's true arterial oxygen saturation is associated with their underlying cardiac-induced pulsatile signals. Nellcor™ pulse oximetry technology focuses on the persistent and generally rhythmic nature of these signals to ensure it measures the oxygenation of arterial blood, as opposed to measuring venous blood, which has low O_2 saturation and little to no pulse as it returns to the heart.

Early Nellcor™ pulse oximetry technology targeted the cardiac portion of the signal by evaluating the beat-to-beat consistency of pulse rate, amplitude, and saturation — later adding arterial pulse shape (heart squeezes fast and refills slow). Nellcor™ pulse oximeters filter out the non-cardiac portion of the signal — caused by artifact due to motion, vasoactivity, and electronic and optical interference — to provide an accurate measure of arterial oxygen saturation.

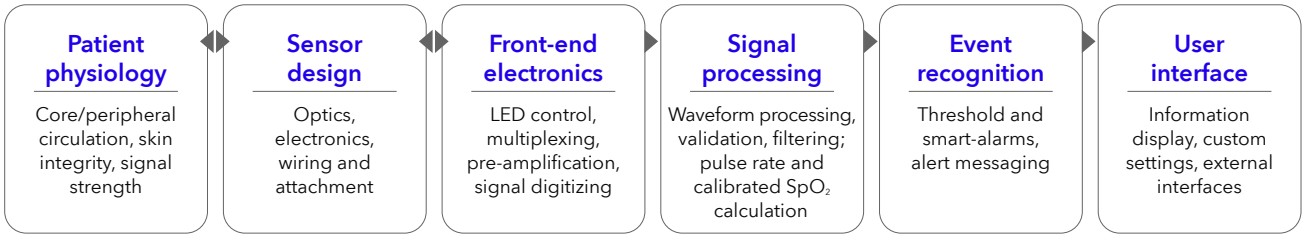

Figure 1. Pulse oximetry technology is a system that assesses a patient's physiological status and communicates those readings to the caregiver. Each aspect of the system contributes to the product's accuracy and reliability.

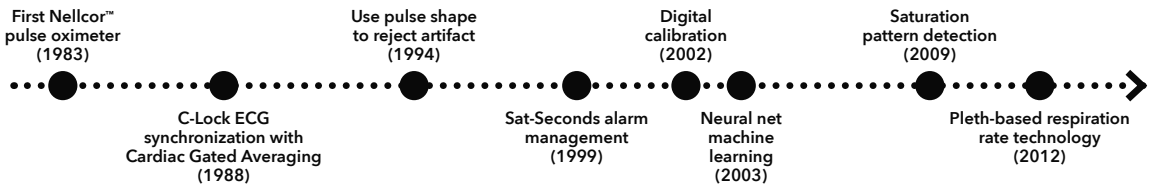

Figure 2. Timeline of technology milestones and advancements in Nellcor™ pulse oximeters. Key advances have been carried forward into subsequent product generations.

Nellcor™ pulse oximetry signal processing algorithms

The signal processing algorithm inside all Nellcor™ pulse oximetry with OxiMax™ technology monitors, OEM boards, and licensed software includes interdependent algorithms to estimate SpO_2 and pulse rate and to shift the beep tone to reflect changes in oxygen saturation (Figure 3).

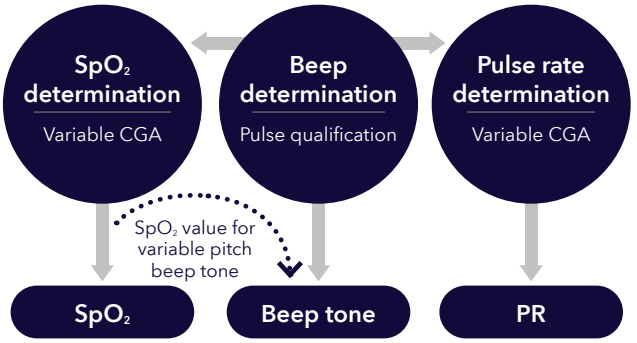

Figure 3. Diagram of Nellcor™ pulse oximetry with OxiMax™ technology signal processing structure.

Because patient waveforms are diverse, they can include dicrotic notches, arrhythmias, motion- and mechanical ventilator-induced artifact, system noise, pulse waveform shape, or morphology differences (based on patient age and whether the sensor is on the head), and the transients and "flat lines" that occur when the sensor slips off. Nellcor™ pulse oximetry technology distinguishes arterial pulses from all these artifacts, regardless of their physiologic or technologic origin.

A key Nellcor™ pulse oximetry with OxiMax™ technology signal processing technique is cardiac gated averaging (CGA) (Figure 4). CGA enhances the ability of the pulse oximeter to provide more reliable saturation measurements during difficult monitoring conditions, including patient motion and poor perfusion.[2]

CGA averages away "noise" frequencies in the optical signal that do not match the heartbeat, so that the system calculates SpO2 and finds pulses from internally processed waveforms that more faithfully represent the arterial pulse.. Current Nellcor™ pulse oximetry with OxiMax™ technology monitoring systems obtain this performance using the optical signal from the sensor (Figure 5).

Besides mitigating multiple types of signal interference, Nellcor™ pulse oximetry with OxiMax™ technology helps reduce clinically insignificant alarms with the Nellcor™ SatSeconds alarm management feature. The Nellcor™ SatSeconds alarm management feature suppresses audible alarms that are too shallow or transient (in combination) to result in interventions while identifying alarm conditions that require intervention.

One study in the NICU found 75% of threshold- defined oxygen desaturations lasted ≤ 10 seconds, and approximately 10% of threshold-defined desaturations were associated with clinical interventions.[3] The Nellcor™ SatSeconds alarm management feature accounts for these short-duration and typically shallow desaturations to reduce alarm frequency while still alerting clinicians to long-duration desaturation events.

Data comparing Nellcor™ pulse oximeter alarms with and

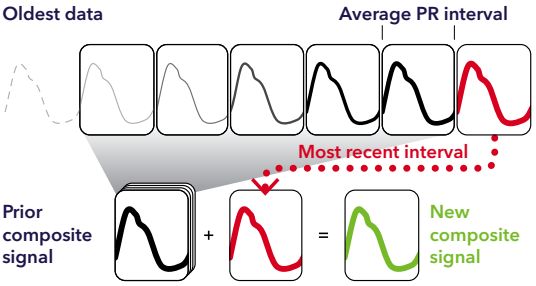

Figure 4. Cardiac gated averaging breaks the incoming signal into segments corresponding to the average heart rate. These segments are numerically combined to create a composite "pulse" signal.

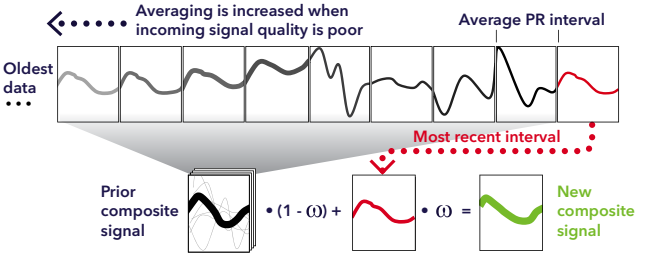

Figure 5. Weighting (ω, spanning approximately 0 to 1) is adjusted when signal interference is present. The parts of the waveform that are synchronous with the average heart rate pass through the CGA process unaffected, while signal portions not occurring with the rhythm of the heartbeat are attenuated.

without Nellcor™ SatSeconds alarm management showed "application of an integrated alarm system at 50 SatSeconds reduces clinically insignificant pulse oximetry alarms by 40% and allows for a new alarm management feature to aid caregivers in responding to potentially clinically relevant alarms."[4]

More recent offerings include the Saturation Pattern Detection™ algorithm (SPD) to advise repetitive SpO_2 swings (which are characteristic of obstructive sleep apnea) as well as pleth-based respiration rate to estimate respiration rate from modulation of the pulse metrics generated by the internal algorithm.

Role of artificial intelligence and machine learning

Artificial intelligence (AI) and machine learning in medical technologies have become an established method to provide more accurate diagnoses. Nellcor™ pulse oximetry technology developed its first AI-enabled products more than 20 years ago with the deployment of a neural network that examines seven signal properties to determine when the sensor has slipped off.

A second neural network used for pulse qualification enhanced the reliability of both pulse rate and beep tone. This neural network examines even more signal properties and was trained on hundreds of thousands of pulses and artifacts that were manually classified from pre-collected oximetry data across a wide range of patient groups, from neonates to adults and patients with certain clinical considerations.

Flexibility of Nellcor™ pulse oximetry with OxiMax™ technology

The Nellcor™ pulse oximeter represents an integrated system that

includes the sensor, cable, complex signal processing algorithms including OxiMax™ technology, and a user interface. Nellcor™ pulse oximetry can be used with a broad range of monitoring and medical device host systems because it supplies its original equipment manufacturer (OEM) boards, technology, and licenses to a large number of medical monitor manufacturers globally, including GE, Philips, Spacelabs, Mindray, and many others.[5] This flexibility means clinicians can expect the same accuracy and reliability from OEM partner monitoring systems.

In addition, Nellcor™ pulse oximetry sensors with OxiMax™ technology are appropriately sized for virtually every patient size and condition. For example, Nellcor™ pulse oximetry sensors have been validated to provide accurate and reliable heart rate during post-delivery moments for newborns[6] and maintain accuracy during motion artifact caused by turning pediatric patients.[7]

Nellcor™ pulse oximetry with OxiMax™ technology systems are equipped with the digital calibration flexibility to enable more accurate forehead SpO_2 measurements in critically ill patients when using the Nellcor™ SpO_2 forehead sensor (MAXFAST).[8-11] The forehead is a sensor site that is physiologically resistant to vasoconstriction and circulatory delays because arterial blood traveling from the heart reaches the head sooner than distal sites such as fingers, especially when patients have poor pulse perfusion.[12] Signal processing is designed to detect changes in SpO_2 earlier than conventional sensors with an accuracy that correlates closer to arterial blood data.

Conclusion

Combined with other flexible system elements, Nellcor™ pulse oximetry has expanded clinical applications for pulse oximetry monitoring to help clinicians provide better patient care with effective monitoring of a broad range of patients, from neonate to adult, and across the continuum of care.

The Nellcor™ pulse oximetry monitoring system should not be used as the sole basis for diagnosis or therapy and is intended only as an adjunct in patient assessment.

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Extending the Benefits of Human Milk-Based Fortification to New Infant Populations

Megan Schmidt, MD and Mary Frances Lynch, MD

The World Health Organization asserts that optimal nutrition in the first weeks and years of life is essential to good health throughout the lifespan. Optimal nutrition in the first 3 years of life in particular reduces the risk of morbidity and mortality and promotes both mental and physical development.[1]

Mounting evidence indicates that an Exclusive Human Milk Diet (EHMD) consisting of mother's own milk (MOM) and/or donor milk (DM) fortified with nutritional fortifier made exclusively from human milk improves outcomes in premature infants born very low birth weight, including a reduction in complications[2-8] and mortality,[4,9] shorter hospital stays,[7] improved feeding tolerance,[10] less time on total parenteral nutrition (TPN),[4] lower healthcare costs,[7,10-12] and better long-term outcomes.[13-15]

New studies and increasing real-world use of an EHMD are also showing similar benefits for term infants born at high risk for feeding intolerance, such as those with surgical gastrointestinal (GI) disorders. Notably, Shinnick et al conducted a retrospective study of 163 infants with an average gestational age (GA) of 36 weeks and birth weight of 2570g admitted within the first week of life to a single center with a diagnosis of a surgical GI disorder. The investigators compared outcomes among those who received 100% human milk (ie, an EHMD), ≥ 50% human milk, and < 50% human milk. Infants fed using an EHMD had a shorter time to full enteral feeds than those whose diets consisted of < 50% human milk (median 21 days vs 32 days; P = 0.023) as well as fewer days on parenteral nutrition (PN) compared with those whose diets consisted of ≥ 50% human milk (median 21 days vs 28.5 days; P = 0.034). In addition, length of hospital stay was 10 days shorter for the EHMD group than the ≥ 50% human milk group and 13.5 days shorter than for the < 50% group (P < 0.05 for both comparisons).[16]

These findings suggest that an EHMD could benefit patients born with gastroschisis, a periumbilical abdominal wall defect that exposes herniated abdominal contents and extruded viscera to the amniotic environment, which produces intestinal damage and dysmotility.[17] These infants typically experience significant feeding intolerance. They can also experience myriad complications that can include intrauterine growth restriction, bowel dilation, intestinal atresia, perforation, and bowel necrosis. The incidence of gastroschisis is increasing,[18] and postnatal management challenges include growth failure, gastric acid hypersecretion/gastroesophageal reflux disease (GERD), dysmotility, and dysbiosis.[17]

Potential role of human milk in gastroschisis

Dysbiosis

Human milk is rich in components that contribute to a healthy gut and immune system. These include immunoglobulins, nucleotides, live cells, growth factors, lactoferrin, and oligosaccharides.[17,19-21] There is evidence that these very components of human milk, which are not reliably present in cow milk-based formula, contribute to gut maturation and development of a healthy microbiome.[22-24] It stands to reason then that an EHMD would support development of a healthy gut microbiome in infants with gastroschisis who are vulnerable to dysbiosis.

Feeding tolerance, days on PN, central line time, and time to discharge

In the very low birth weight (VLBW) premature infant population, the use of human milk has been shown to improve feeding tolerance, reduce time on PN, and shorten time to full enteral feeds.[4,10,25-27] Similar to premature and VLBW infants during their first weeks of life, infants with gastroschisis require intensive nutritional support to facilitate healthy growth and are similarly vulnerable to prolonged exposure to PN and associated complications.

A rapid transition to full enteral feedings is a similarly important goal in the gastroschisis patient population. Delays in enteral feeding means these infants have delayed exposure to trophic factors that can counteract dysbiosis. The especially high need for antibiotics in this patient population further promotes dysbiosis. Observational studies demonstrate that each day of delay in initiation of enteral feeding among infants with gastroschisis increases total PN by 1.55 days and length of hospital stay by 1.39 days.[17] In one such study, 22 infants with gastroschisis who received early minimal enteral feeding (defined as enteral nutrition initiated 5 days after bowel

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reintegration and increasing by 12 mL/kg/day) were compared with 51 controls, in whom enteral nutrition was delayed until resolution of postoperative ileus, and increment of feeding was not systematized. Time to first enteral nutrition was significantly shorter in the early enteral feeding group (5 days vs 11.5 days; P = 0.0005), and this group had a significantly reduced incidence of nosocomial infection (9% vs 40%; P = 0.016) and a trend toward shorter hospital stay (40 days vs 54.5 days; P = 0.08) than controls.[28]

Studies on the use of human milk in patients with gastroschisis have shown potential benefits in terms of feeding tolerance and time to discharge. A retrospective study of 44 infants with gastroschisis revealed that feeding with MOM after surgical repair was associated with shorter time to discharge from feeding initiation (adjusted hazard ratio [HR] for discharge per 10% increase in MOM dose 1.111; 95% CI 1.011–1.220; P = 0.029). In addition, MOM dose was significantly associated with shorter length of hospital stay (adjusted HR for discharge per 10% increase in MOM dose 1.130; 95% CI 1.028–1.242; P = 0.011).[29] Similarly, a multi-institutional database review demonstrated among 3062 patients who underwent gastroschisis repair that enteral feeding using human milk (MOM or DM) vs formula was associated with a shorter time to hospital discharge, in a dose-dependent manner.[30] Another retrospective study, this time among 44 infants born ≥ 33 weeks GA with a birth weight of > 1500 g who had gastroschisis or small bowel atresia had a shorter median length of stay (25 days vs 35 days; P < 0.01) and fewer central line days (20 days vs 28 days; P < 0.01) when they received DM to supplement MOM rather than formula.[31]

Balancing complications and growth

Intrauterine growth restriction is common in gastroschisis, with nearly half of these infants being born in the 10 percentile or lower for weight.[32] A California cohort study revealed that 55% of infants with gastroschisis had a weight or length growth failure at discharge.[33] Thus, safely providing optimal nutrition as quickly as possible is a priority in the first days and weeks of life.

While PN can provide needed nutrition, longer time on PN is associated with significant complications.[34] As previously discussed, the use of human milk reduces time on PN in preterm infants born VLBW as well as in term infants with gastroschisis. In the VLBW population, less time on PN has also been linked with healthier growth metrics[13-15] as well as better long-term neurodevelopmental outcomes.[35,36] Use of nutritional fortifiers is an important way to provide the intensive nutrition needed to promote healthy growth without resorting to long periods on TPN. An EHMD using a nutritional fortifier made from human milk has been shown to improve growth metrics in VLBW premature infants,[37] with earlier nutritional fortification being superior to later fortification.[38] Could an EHMD that includes use of human milk-based nutritional fortifiers offer similar benefits in gastroschisis? The evidence suggests it could.

A multicenter randomized clinical trial (NCT02567292) evaluated the benefits of an EHMD in patients with congenital gastrointestinal disorders. Nutritional fortifier made exclusively from human milk and formulated for the nutritional needs of term babies was used. It demonstrated that using an EHMD, compared with formula, significantly reduced the overall risk of necrotizing enterocolitis (NEC) (2.0% vs 7.8%) and significantly improved WFL z-scores, direct bilirubin, and clinical sepsis.[39]

Better postoperative feeding protocols

Following surgery for gastroschisis, the goal is to wean patients off PN as quickly as possible. To do so, standard nutritional guidelines are used, but they are not optimized for this specific patient population. Starting enteral feeding 7-21 days postsurgically is recommended,[40] but there is mounting evidence that starting as early as 24-48 hours is also safe and promotes better outcomes.[33,41] Hair and Good have suggested a tiered feeding protocol for infants with intestinal failure that divides infants into high, medium, and low risk for undernutrition and development of complications.[42]

Given that up to half of infants born with gastroschisis are also premature,[43] it seems likely that feeding protocols designed for preterm infants could benefit infants with gastroschisis as well. As we have seen, protocols that highlight an EHMD greatly benefit the VLBW preterm population. In addition, there is evidence that individual hospital postsurgical feeding protocols for infants with gastroschisis that prioritize the use of human milk have been associated with better outcomes in this patient population.[40]

Case study

For the reasons outlined above, we opted to try an EHMD, consisting of human milk-based fortifier in addition to MOM, to reduce hospital-acquired undernutrition for an uncomplicated case of simple gastroschisis being treated at our Level III 64-bed NICU. The patient was diagnosed prenatally with gastroschisis and born vaginally after induction at 36 weeks and 3 days due to maternal fever, growth restriction, and non-reassuring fetal heart tones. The infant's birth weight was 2260 grams, length was 45 cm, and frontal occipital circumference (FOC) was 32 cm.

The infant underwent silo placement with serial bowel reductions by pediatric surgery, with sutureless surgical closure on day of life (DOL) 5 without complications. We supported nutrition with TPN until bowel function allowed enteral feeding, which was started successfully with unfortified MOM on the 18th day of life. Feeding was then advanced based on the infant's tolerance. We began fortification with a human milk-based fortifier when feeds reached 50 ml/kg, which mimicked our NICU's fortification guideline for premature infants. Full enteral feedings of 140 ml/kg were reached on DOL 25. On DOL 27, the patient's feeds were changed to ad libitum unfortified MOM or feeding at the breast, and fortifier was discontinued. This led to a slight decrease in weight, despite the patient consuming appropriate volumes for age of MOM, prompting supplementation with 22 kcal/ounce of elemental formula (Elecare) 4 times daily on DOL 32. Weight increased without signs of feeding intolerance, and the patient was discharged home on DOL 33 (gestational age 41 weeks, 1 day).

At discharge, the patient weighed 2934 grams with an FOC of 34.5 g and length 48 cm. At this time, the patient did not meet criteria for malnutrition. One month later, on DOL 54, Elecare supplementation was discontinued based on excellent growth and a weight of 3520 g.

Compared with a recent historical cohort in our NICU, this infant had several improved outcomes. These included

discharge with no clinical signs of malnutrition, only 12 days to full feeds (vs 22.4 in the cohort group), shorter length of hospital stay (33 days vs 51.5 days), and fewer TPN days (25 days vs 36.5 days). The patient's peak direct bilirubin was comparable to the historical cohort at 1.5 mg/dL.

Conclusions

There is evidence that an EHMD consisting of MOM/DM plus nutritional fortifier made exclusively from human milk improves short- and long-term outcomes in premature infants born VLBW. Because of key similarities between these infants and those with gastroschisis, there is good reason to believe that an EHMD would also benefit infants with gastroschisis, even if they are born at term. Our case study supports this assertion. There is a need for further research into the benefits of an EHMD among term infants born with GI and other congenital abnormalities.

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An Unusual Case of Severe Asphyxia With the Fetal Position Unexpectedly Inverted in a Malformed Uterus: A Case Report

Jiro Abe,[1,2,3] Takashi Nasu,[1] Ayumu Noro[1] and Junko Tsubaki[1]

Abstract

Background. We present a severe neonatal consequence due to the unexpected and crucial inversion of the fetal position after sudden termination of tocolysis during early labor of a woman with congenital uterine anomaly. It has been reported that congenital uterine anomalies latently affect the fetal position. The clinical pitfalls in childbirth with uterine anomalies are discussed here on the basis of clinical evidence.

Case presentation. At a perinatal medical center in Japan, a 29-year-old Japanese mother who had a history of bicornuate uterus, received tocolysis to prolong her pregnancy for 5 days during the late preterm period after pretermprematurе rupture of the membrane. She gave birth to a 2304 g male neonate of the gestational age of 35 weeks and 5 days with severe asphyxia by means of crash cesarean section for fetal sustained bradycardia after sudden termination of tocolysis. We found the fetal position to reverse from cephalic to breech position during early labor. He ended up having severe cerebral palsy after brain cooling against hypoxic-ischemic encephalopathy for 3 days. The mechanism of inversion from cephalic to breech position without amnionic fluid remains unclear, although women with a known diagnosis of a uterine anomaly have higher risk of adverse outcomes such as malpresentation.

Conclusions. When considering the clinical course of this case on the basis of the medical reports, we suspected that uterine anomalies and changes in intrauterine pressure could cause fetal malpresentation and adverse neonatal outcomes.

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Background

Uterine abnormalities may be overlooked in women with successful reproductive outcomes, but one study estimated that, even in women with normal pregnancy outcomes, the incidence of congenital uterine anomalies is approximately 3%. The likelihood of fetal malpresentation at the time of delivery is notably increased by the presence of uterine anomalies.[1]
A case is presented where a mother with bicornuate uterus received tocolytic treatment with β-stimulants after surpassing 35 weeks of gestation. Following the discontinuation of tocolysis associated with the onset of labor, the fetus experienced distress and malpresentation, ultimately resulting in severe cerebral palsy in the child. There are no existing case reports that show a change in fetal presentation during labor with uterine anomalies resulting in fetal asphyxia.

Case presentation

A 29-year-old Japanese mother who had a history of bicornuate uterus gave birth to a 2304 g male neonate of the gestational age of 35 weeks and 5 days with severe asphyxia. She was a primigravida without health issues, and her pregnancy course, including changes in maternal body mass index (BMI) and gestational weight gain, was smooth. She was admitted to our hospital to receive tocolysis treatments using ritodrine hydrochloride because of preterm premature rupture of membrane at 35 weeks' gestation, receiving antibiotics, no antenatal corticosteroids, and no magnesium sulfate. The ultrasound examinations revealed overall fetal growth, reduced amniotic fluid, and a fetal vertex position. A total of 3 hours before the birth, the administration of the tocolytic agent, by ritodrine hydrochloride using the maximum dose of 200 μg per minute, was terminated to promote vaginal delivery, and she was transferred to a delivery room. Non-reassuring patterns repetitively emerged at 1 hour prior to the birth, which were only confirmed by cardiotocography without an ultrasound examination performed at that time (Fig. 1A). General fetal resuscitation such as maternal oxygen administration and intravenous infusion of a liter of non-glucose crystalloid without acute tocolysis was used as part of the obstetric management of labor, while preparing for cesarean delivery for fetal distress. Quick pelvic examinations ensured the fetus's cephalic position while observing the mother in preparation for an emergency cesarean operation, although the fetal position during delivery was not confirmed by ultrasound. Half an hour before the birth,

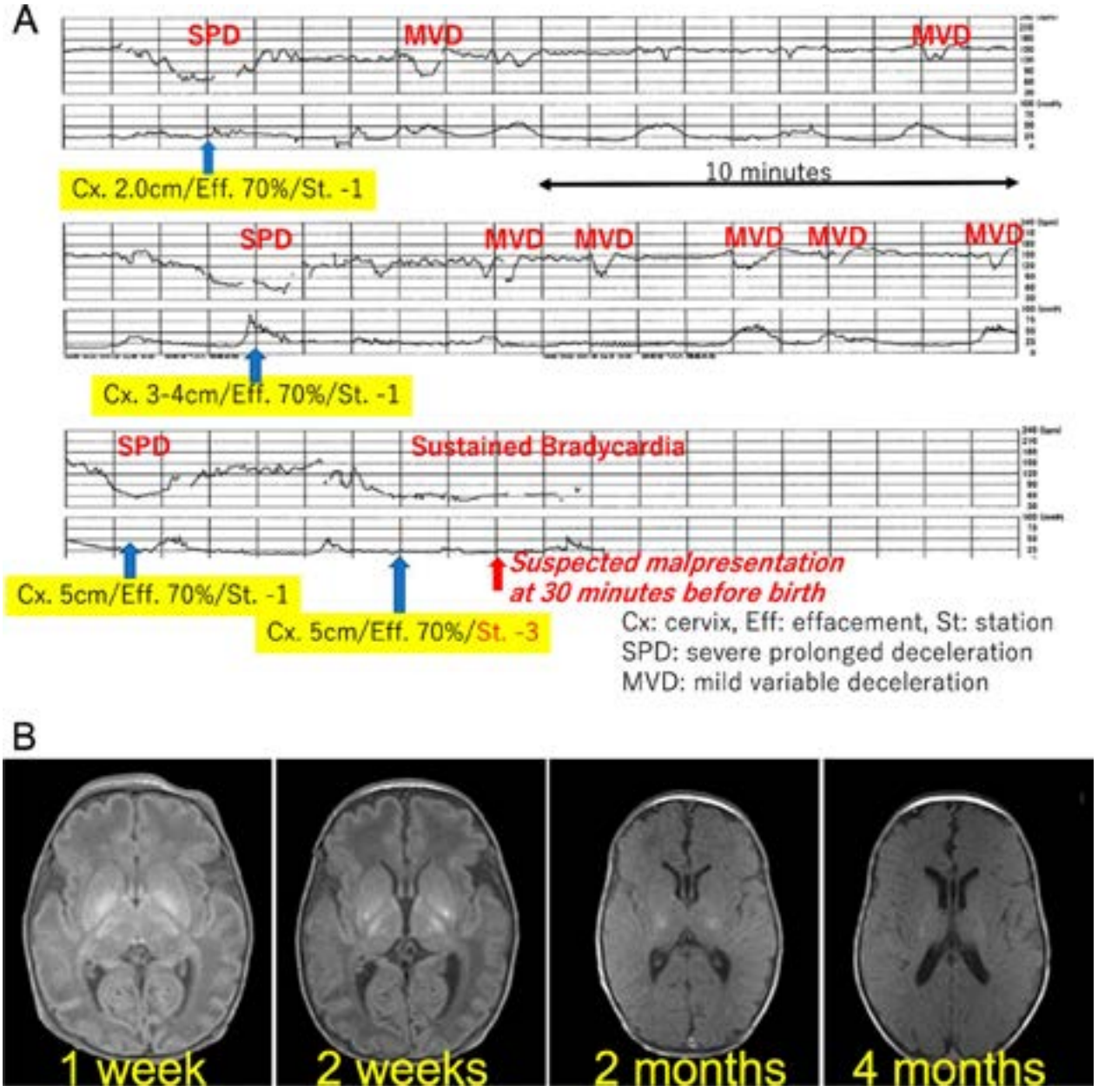

Fig. 1 (A) Cardiotocography immediately before birth. Non-reassuring patterns repetitively emerged 1 hour prior to birth. Pelvic examinations revealed a fixed cephalic position. At half an hour, fetal bradycardia was sustained while the pelvic examination indicated that the fetal head was unexpectedly floating. (B) Sequential brain magnetic resonance imaging (MRI). According to sequential brain MRI findings, his lesions post hypoxic-ischemic encephalopathy (HIE) were mainly located in the basal ganglia and the brain stem

fetal bradycardia was sustained while the pelvic examination indicated that the fetal head was unexpectedly floating (Fig. 1A). A crash cesarean section was performed, where he was found to be in a breech presentation. We found quite little amniotic fluid without the evidence of meconium-stained amniotic fluid or cord coiling. The pathological findings of the placenta and umbilical cord proved only mild chorioamnionitis without any evidence of delivery injury or anomaly afterward.

After delivery he presented with bradycardia and deep cyanosis without breathing, muscle movements, and reflections. Because his asphyxia turned out to be refractory to routine resuscitation, he was intubated after 1 minute. His skin color rapidly became pink, and the heart rate returned to a normal range without the recovery of muscle movements and reflex actions. He received an appearance, pulse, grimace, activity, and respiration (APGAR) score of 1 at 1 minute and 3 at 5 minutes; the arterial cord blood sample was not available, because of tecÚical difficulty in sampling umbilical cord blood. He needed special care that included mechanical ventilation and correction of mixed acidosis (pH 6.85, pvCO2 77 mmHg, HCO_3 12.6 mmol/l at 15 minutes after birth), and then he was given phenobarbital. At 1.5 hours after birth, he was transferred to another tertiary care hospital where he received therapeutic hypothermia for hypoxicischemic encephalopathy; the Sarnat grade was moderate, and the Thompson score was calculated as 16 points.[2] He was a late preterm and low-birth-weight newborn with no congenital anomalies or other problems that would be predictive of neonatal asphyxia through newborn screening especially focusing on the brain, heart, or metabolism. We could not find clinical and pathological evidence of his severe asphyxia in the end. Chromosomal testing was not conducted. He ended

up having severe cerebral palsy after brain cooling for 3 days. His sequential brain MRI findings supported the severity of the encephalopathy that mainly affected the basal ganglia and brain stem (Fig. 1B). He is now 9 months of age and remains in bed with special healthcare requirements that include tube feeding, while presenting with dystonia with severe mental developmental retardation.

Discussion and conclusions

The mother had some delivery risks as follows: a uterine anomaly, absent amniotic fluid after preterm-premature rupture of membrane, and threatened late-preterm labor. The placental blood flow in mothers with congenital uterine anomalies is reduced, and there is a predicted decrease in the reserve capacity for blood supply to the fetus, particularly during delivery. When a mother has congenital uterine anomalies, there is a 5-fold increased risk of preterm birth and a 20-fold increased risk of placental abruption.[3] This case is believed to be caused by circulatory insufficiency between the mother and fetus, with the influence of congenital uterine anomaly likely playing a background role. Increased intrauterine pressure might have occurred by abrupt termination of tocolysis with the lack of amniotic fluid, which would make the fetal status worse, although there was no evidence of excessively rapid uterine contractions in the tocography (Fig. 1A).

Fig. 1 (A) Cardiotocography immediately before birth. Non-reassuring patterns repetitively emerged 1 hour prior to birth. Pelvic examinations revealed a fixed cephalic position. At half an hour, fetal bradycardia was sustained while the pelvic examination indicated that the fetal head was unexpectedly floating. (B) Sequential brain magnetic resonance imaging (MRI). According to sequential brain MRI findings, his lesions post hypoxicischemic encephalopathy (HIE) were mainly located in the basal ganglia and the brain stem.

Uterine anomalies are known to significantly elevate the chances of fetal malpresentation during delivery. According to the meta-analysis by Chan, the likelihood of fetal malpresentation was found to be higher in cases of arcuate uterus, unification defects, and canalization defects, with the odds being 2.53 [95% confidence interval (CI) 1.54–4.18; $p < 0.001$], 3.87 (95% CI 2.42–6.18; $p < 0.001$), and 6.24 (95% CI 4.05–9.62; $p < 0.001$) times, respectively.[4] Furthermore, a retrospective study by Hua and colleagues, which encompassed all types of uterine anomalies (including uterine septum, unicornuate uterus, bicornuate uterus, and uterine didelphys), revealed that women with these anomalies were 8.6 times more likely to experience breech presentation of the fetus compared with women with standard uterine anatomy (95% CI 6.2–12.0; $p < 0.01$).[5] Additionally, a comprehensive retrospective cross-sectional study, examining a total of 109,736 singleton infants (both preterm and full-term), of which 4535 were breech at birth, determined that women with any form of uterine malformation had an almost 10-fold increase in the likelihood of breech fetal presentation (odds ratio, 9.47; 95% CI 6.77–13.25).[6] Possible causes are thought to be changes in intrauterine and external pressure, for example, the effects of uterine malformations, the sudden discontinuation of uterine contraction inhibiting drugs, and the transfer from the delivery table to the bed. The unexpected inversion of the fetal position with very little amniotic fluid during early labor would have led to the poor consequence, causing the umbilical cord to twist and consequently leading to the interruption of placental blood flow.

It may have been unavoidable, but we can suggest two preventive plans for this case. One plan would be ongoing expectant management with or without tocolysis. The issue of whether to suppress or allow progressive labor to proceed during the late-preterm period remains controversial.[7] If waiting for labor while inhibiting uterine contractions, it is necessary to carefully monitor changes in intrauterine pressure when stopping tocolytic agents. The other one would be planned earlier delivery including elective cesarean operation. Bicornuate uterus has been reported to be a risk factor for unsuccessful vaginal delivery.[8] A major meta-analysis discovered that the likelihood of undergoing a primary cesarean delivery was 2.6 times higher for women with congenital uterine anomalies (adjusted odds ratio [aOR], 2.6; 95% CI 1.7–4.0; $p < 0.01$).[5] Additionally, a retrospective cohort study over a decade at a French university hospital assessed women known to have uterine malformations, focusing on the baby's presentation and the method of delivery. In this group, women with uterine abnormalities showed a significantly increased incidence of breech presentations (36.51% as opposed to 4.52%; $p < 0.01$) and cesarean deliveries (55.26% compared with 18.70%; $p < 0.01$), in contrast to women with normally formed uteri.[9]

Women with congenital uterine anomalies face significantly higher risks of preterm birth, placental abruption, fetal malpresentation, and breech presentation. Several studies highlight the increased odds of complications such as fetal malpresentation and breech births, indicating a need for careful monitoring and possibly alternative delivery plans, including elective cesarean operations. Our report concludes with suggestions for managing such high-risk cases, emphasizing the importance of careful monitoring or possibly opting for an earlier planned delivery to mitigate risks.

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Author contributions

Jiro Abe designed and prepared the manuscript; Takashi Nasu, Ayumu Noro, and Junko Tsubaki provided tecÚical support and conceptual advice. All of the authors read and approved the final version of the manuscript.

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Availability of data and materials

The approval from the parent allowed us to use the patient's data and report this case with data anonymization.

Declarations

Ethics approval and consent to participate

We strictly followed the rules for publication by the research ethics committee in Hokkaido University Hospital, which permitted us to participate.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

We have no competing interests.

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Congenital Herpes Simplex With Ophthalmic and Multisystem Features: A Case Report

Samuel Montenegro Pereira, Rian Vilar Lima, Maria Carolina Rocha Muniz, Marcus Breno Farias Araújo, Luiz de Moraes Ferreira Júnior, Juliana Tiburtino de Queiroz Sales Martins, Cláudia Faustino Coelho Luz, David Antônio Camelo Cid and Daniel da Rocha Lucena

Abstract

Background. Neonatal herpes simplex virus (HSV) infection is rare and has significant morbimortality rates. Approximately 85% of newborns are infected intrapartum, and risk factors for mother-to-child transmission include vaginal delivery, primary maternal infection, and prolonged rupture of membranes. Neonatal HSV can manifest with isolated mucocutaneous lesions, neurological involvement, or disseminated disease. In general, herpetic infection can cause blepharoconjunctivitis or keratitis. We report a rare case of congenital herpes with ophthalmologic manifestations and multisystemic involvement.

Case presentation. A preterm infant, born at 32 weeks and 2 days, with presumed neonatal infection developed intestinal and respiratory complications, as well as hyperemic lesions on the left nostril and oral mucosa. An ophthalmological assessment was requested and brought up the suspicion of HSV infection, indicating empirical treatment with endovenous acyclovir. Later, a new ocular examination was suggestive of panuveitis. Afterward, serum IgM antibodies to HSV-1 and HSV-2 were positive. Proper antiviral therapy led to an improvement in the condition.

Discussion. Neonatal herpes is associated with a high risk of persistent skin lesions, long-term neurological disability and other lasting sequelae. It is essential to consider HSV infection in cases of neonatal conjunctivitis, especially in patients with an epithelial defect and no improvement after initial treatment with topical or systemic antibiotics.

Conclusions. In the management of neonatal HSV, early diagnosis is essential for the timely initiation of antiviral therapy. Our report highlights that ocular assessment can be crucial in the correct diagnostic investigation of this condition.

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Background

Neonatal herpes simplex virus (HSV) infection is rare and has variable epidemiology worldwide due to different birth rates and diverse viral seroprevalence.[1] Despite the important advances made in perinatal care over the years, the disease is still associated with significant morbidity and mortality.[2] The estimated annual incidence is variable, ranging between 1.6 and 8.4 per 100,000 live births.[3] Both serotypes, HSV-1 and HSV-2, are related to neonatal infections, although the risk of mother-to-child transmission is considerably higher with HSV-1.[4,5]

Although in most cases the method of transmission is not well established, it is estimated that approximately 85% of babies are infected intrapartum, 10% in the postnatal stage and 5% in utero.[5] Most women who transmit HSV to their children have no documented history of genital herpes, either due to the absence of lesions or the subtlety of the symptoms, which leads to misdiagnosis.[6] The main risk factors associated with neonatal exposure include vaginal delivery, primary maternal infection and prolonged rupture of membranes.[7]

Neonatal HSV can manifest with isolated mucocutaneous lesions, neurological involvement, or disseminated disease.[8] In most cases, these clinical syndromes have overlapping features, that is, they can develop simultaneously. Regarding

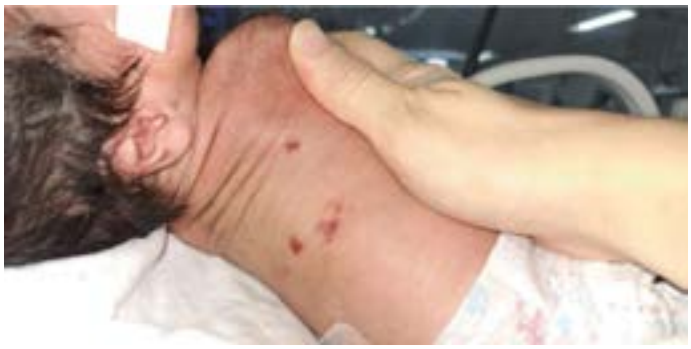

Figure 1. Papulopustular lesions on the back.

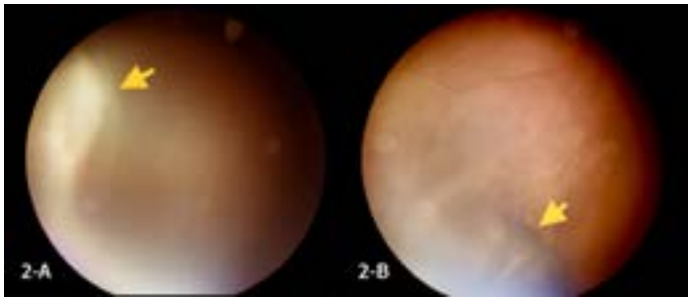

Figure 2. A: Appearance of active retinal necrosis (yellow arrow) in the right eye (RE); 2-B: Retinography with sequelae of retinal necrosis in the RE in the same visit.

ocular manifestations, overall, herpetic infection can cause blepharoconjunctivitis or keratitis, with chorioretinitis or optic atrophy being rare conditions.[9] Given the high mortality rates and potential for long-term repercussions, early diagnosis and timely antiviral treatment are essential for better clinical outcomes.

We report a rare case of congenital herpes with ophthalmologic manifestations and multisystemic involvement, highlighting the major role that ophthalmologic evaluation had in the management of the patient.

Case presentation

The preterm male infant was born at 32 weeks and 2 days by a vaginal delivery 18 h after rupture of the membranes, with a birth weight of 2.092 g and an Apgar score of 6/8 at 1 and 5 min, respectively. The mother denied former or current use of drugs or medications but reported inadequate prenatal care, with only one medical visit made throughout pregnancy and no serology exams performed. At hospital admission, she had only a reactive VDRL result of 1:1 and revealed treatment for syphilis in prior pregnancy, raising the possibility of a serological scar. On examination, she presented only nonspecific lesions in the genital area. The clinical hypothesis of neonatal infection was brought up, antibiotic therapy was started, and infectious screening, lumbar puncture (LP), and cranial computerized tomography (CT) scan were indicated for the newborn.

Serial blood cultures were performed throughout the hospital stay, including on admission, but were persistently negative. Cerebrospinal fluid (CSF) analysis showed the following: proteins = 110 mg/dL; 80 cells per mm3; red blood cells (RBC) = 12,000; VDRL negative. No changes in medical management were made on account of these findings. Some days later, the baby was transferred to the neonatal intensive care unit (ICU) due to abdominal distension, bloody gastric residuals and respiratory distress. The next day, papulopustular lesions emerged on the back and chest (Figure 1). Afterwards, the infant suffered further episodes of apnea, cyanosis and bradycardia. Thus, the antibiotic regimen was optimized for a wider spectrum, and mechanical ventilation was indicated. Later, hyperemic lesions were identified in the left nostril and on the oral mucosa.

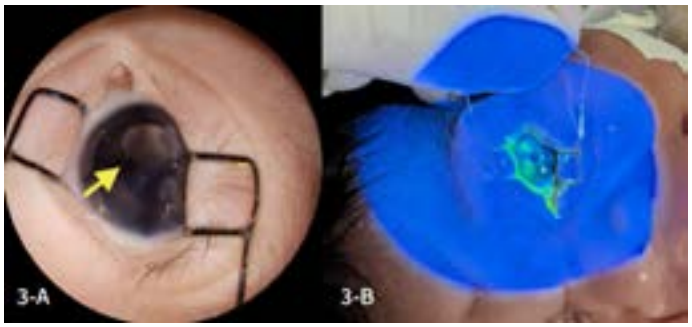

Figure 3. A and 3-B: Extensive corneal opacity and irregular, superficial, fluorescein-stained posterior synechiae, indicating epithelial keratitis with a dense infiltrate, mainly affecting the upper paracentral and peripheral regions of the left eye.

An ophthalmologic assessment was requested, revealing in the right eye (RE) signs suggestive of retinal necrosis in the superior temporal region (Figure 2-A) and pigmented areas in the inferior portion of the retina (Figure 2-B), which was impossible to perform in the left eye (LE) due to corneal edema (1+/4+) and vitreous opacification. External eye examination detected mild hyperemia, palpebral edema, and an irregularly shaped fluorescein-stained corneal lesion in the LE, suggestive of panuveitis (Figure 3-A and 3-B).

The suspicion of congenital neonatal infection was raised, with a strong suspicion of HSV. Empirical treatment with intravenous acyclovir was started, and additional serologies were collected to investigate toxoplasmosis, rubella, human immunodeficiency virus (HIV), hepatitis B, syphilis and cytomegalovirus. Due to the ophthalmic findings in the RE (Figure 3-B), it was decided to start topical treatment with moxifloxacin 5 mg/ml, initially with 1 drop every 3 h for 5 days, then 1 drop every 6 h for another 10 days and artificial tears (sodium hyaluronate 0.15%) every 2 h for the same period.

Afterward, serum immunoglobulin M (IgM) antibodies to HSV-1 and HSV-2 were positive. Immunoglobulin G (IgG) and IgM for toxoplasmosis, HIV, hepatitis B, syphilis, rubella, and cytomegalovirus were all negative. A cranial CT scan demonstrated sequela findings secondary to neonatal hypoxic-ischemic encephalopathy, in addition to areas of calcification in the periventricular white matter and nonhypertensive dilatation of the supratentorial ventricular system (Figure 4). A new ophthalmological assessment was performed, which showed no progression of necrosis or new lesions in the RE, as well as regression of corneal edema and no lesions in the LE. Intravenous acyclovir was continued for an additional 28 days, followed by oral acyclovir.

A few weeks later, the baby developed abdominal distension, regurgitations, and fecal vomiting. Abdominal ultrasound revealed free fluid in the cavity and intestinal obstruction, requiring surgical intervention. Drainage of voluminous gastric content was performed, and an inflammatory lesion of nonspecific aspect and stenosis in the terminal ileum were identified, requiring resection of 15 centimeters of the ileum. The result of the intraoperative biopsy showed enteric transmural necrosis, indicative of necrotizing enterocolitis.

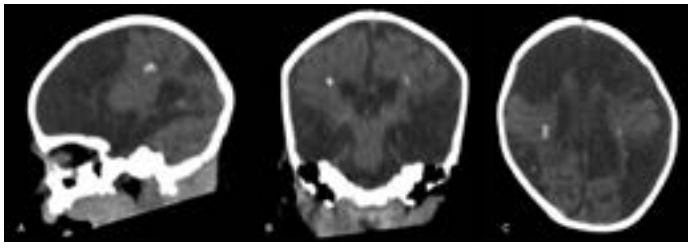

Figure 4. CT scan demonstrating extensive hypodense areas affecting the white matter, multiple areas of parenchymal cystic replacement with sequel-like aspect (cystic leukomalacia), volumetric reduction of the brain and brainstem, and bilateral periventricular foci of calcification; (A) Sagittal, (B) Coronal, and (C) Axial cuts.

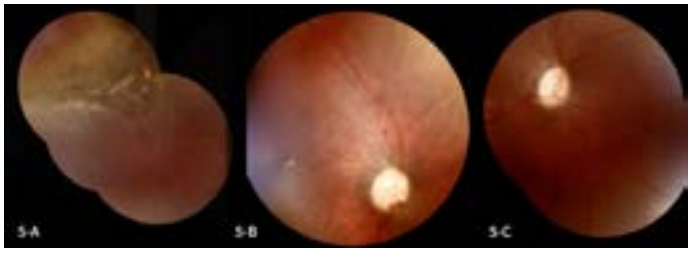

Figure 5. 5-A and 5-B: Retinal images showing the periphery (A) and posterior pole (B) of the right eye at the end of treatment; 5-C: Retinography demonstrating the integrity of the posterior pole of the left eye at the end of treatment.

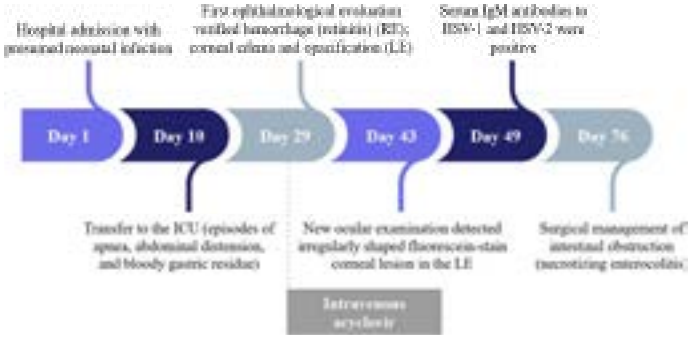

Figure 6. Timeline highlighting the patient's main clinical features and the role of ophthalmologic evaluation in the diagnosis and proper treatment.

Abbreviations: Intensive care unit (ICU); Right eye (RE); Left eye (LE)

A new ophthalmological examination revealed extensive retinal necrosis in the posterior segment of the RE, with no signs of activity and slight pigmentation near the optic disc in the RE (Figure 5-A and 5-B). Despite the severity of the newborn's condition, treatment with acyclovir made it possible to preserve the integrity of the posterior pole of the RE and prevent the spread of infection to the LE (Figure 5-C). In the patient's case, adequate antiviral therapy led to an improved prognosis. An overview of the patient's clinical evolution is depicted in Figure 6.

At the last ophthalmological follow-up, the patient was 8 months old. In the ocular assessment, the child showed interest in objects > 10 cm in diameter.

Discussion

Despite being a rare condition, neonatal HSV infection is one of the most important and challenging differential diagnoses in paediatrics.[8] The disease is a costly condition given that possible complications are associated with long hospital stays, continuous monitoring, prolonged drug treatment, and periodic imaging and laboratory tests.[10] Neonatal herpes has high fatality rates, and even with adequate treatment, patients are at risk for persistent skin lesions, long-term neurological disability, and other lasting sequelae.[8]

Due to the immaturity of the immune system, prematurely born babies have a higher risk of developing complications from bacterial and viral infections.[2] The risk of transmission of HSV from mother to neonates is greater if the maternal infection is primary since there is insufficient time for transplacental passage of immunoglobulins.[11] In mothers with prolonged infection, it is likely that antibody transfer to the fetus will occur, acting as immunoprophylaxis.[12] Additionally, the risk of neonatal herpes is significantly higher in primary maternal infections near term, as there is no time for an effective immune response against the virus.[4]

Congenital herpes simplex is typically diagnosed in newborns after 10 days of age, and the clinical picture comprises the following forms: skin, eye, and mouth (SEM); central nervous system (CNS) impairment; and disseminated disease.[3] Mucocutaneous lesions, usually found as vesicles in the mouth or on the skin, are the most common feature, accounting for approximately 45% of cases.[2] Neonates with neurological involvement account for about 30% of the cases and may manifest irritability, seizures, lethargy, and poor feeding.[11]

Disseminated disease is the most severe form, accounting for approximately 25% of infections, and is related to multisystem involvement.[3] In our case, necrotizing enterocolitis stood out as a complication that, although not usually associated with HSV infection, is known to have a multifactorial etiology and may have been precipitated by the condition.[13] HSV manifestations can be mistaken for bacterial sepsis or metabolic disorders due to the patient's poor appearance and multiorgan symptoms.[11]

Differential diagnosis with the group of the most common congenital infections, referred to by the acronym TORCH, remains an aspect of essential consideration, especially in cases with multiple clinical features. However, the classic approach to this investigation, which focuses on serological tests, has been questioned by recent literature, which now advocates a multimodal evaluation that includes radiology, ophthalmology audiology, microbiology, and polymerase chain reaction (PCR) testing, both for infant and placental tissue.[14] Although our case is a satisfactory example of the effectiveness of this approach, we recognize that the applicability of this trend in the literature can be difficult in the majority of low-resource centers, where PCR is not widely available and a multidisciplinary team may not be present.[10]

Herpes simplex eye disease can result in cataracts, corneal ulceration, anterior uveitis, vitritis, chorioretinitis, and optic atrophy and is the main cause of corneal visual loss in developed countries.[9,15] In the acute phase, conjunctivitis is the most frequent ophthalmologic symptom in neonates and is often associated with herpetic epithelial keratitis.[16] Corneal involvement, as in our case, is unilateral in approximately 90% of patients.[15] Considering that there is potential clinical overlap with other etiologies of conjunctival disease, such as gonococcal disease, diagnosis can be challenging.[6] Hence, it is essential to consider HSV infection in cases of neonatal conjunctivitis, especially in patients with an epithelial defect and no improvement after empiric treatment with topical antibiotics.[16]

Early diagnosis is essential to improve prognosis but demanding, given the nonspecificity of clinical signs and the challenges of managing neonatal patients. The American Academy of Pediatrics Committee on Infectious Diseases recommends, among other tests, viral culture and PCR of swabs of conjunctiva, CSF, HSV PCR, and serum HSV PCR for evaluation of neonates with suspected diagnosis.[11] Treatment with high-dose intravenous acyclovir (60 mg/kg/day) decreases mortality, reaching 4% in CNS impairment and 30% in disseminated disease, and should extend to at least 21 days in these cases.[11] Afterward, suppressive therapy with oral acyclovir is recommended for a 6-month course.[11]

The evolution of the patient demonstrates the importance of considering HSV disease in the range of neonatal infections. The newborn's clinical picture was marked by multiorgan complications and extensive ocular involvement, with potentially serious long-term sequelae. Additionally, it highlights the role of ophthalmologic assessment in the diagnostic investigation since it guides the clinical judgment toward the correct hypothesis and enables appropriate therapeutic conduct.

Conclusions

Prevention measures of mother-to-child transmission are essential for decreasing the prevalence and morbimortality rates of congenital herpes. In the management of neonatal HSV, early diagnosis is essential for the timely initiation of antiviral therapy, which decreases the risk of associated complications. Especially in cases of disseminated disease, the neonate should be followed up not only by the pediatrician but also by the ophthalmologist for evaluation of the recurrence of symptoms, sequelae, or side effects of medications. Our report emphasizes that ocular assessment can be central in the diagnostic investigation of this condition and in improving the patient's prognosis.

List of abbreviations

HSV	Herpes simplex virus
LP	Lumbar puncture
CT	Computerized tomography
CSF	Cerebrospinal fluid
RBC	Red blood cells
ICU	Intensive care unit
RE	Right eye
LE	Left eye
HIV	Human immunodeficiency virus
IgM	Immunoglobulin M
IgG	Immunoglobulin G
SEM	Skin, eye, and mouth
CNS	Central nervous system
PCR	Polymerase chain reaction

Data availability

The data supporting the findings of this case report are available from the corresponding author upon reasonable request.

Authors' contributions

S.M.P.: ophthalmologist responsible for patient care; acquired the medical records, fundoscopy exams and images of the case; reviewed and approved the final manuscript. R.V.L.: wrote the abstract and the first version of the manuscript and participated in the graphic editing of Figures 1 to 3. M.C.R.M.: wrote the final version of the manuscript, edited Figures 4 and 5, and developed Figure 6. M.B.F.A.: pediatrician and one of the neonatology residents responsible for patient care; participated in the acquisition of Figure 4 and reviewed the final version of the manuscript. L.M.F.J.: neonatologist pediatrician responsible for patient care and writing of part of the medical records; reviewed and approved the final version of the manuscript. J.T.Q.S.M.: neonatologist pediatrician responsible for patient care and writing of part of the medical records; reviewed and approved the final version of the manuscript. C.F.C.L.: pediatrician and one of the neonatology residents responsible for patient care; reviewed and approved the final version of the manuscript. D.A.C.C.: ophthalmologist responsible for patient care; participated in the description of fundoscopy exams, and reviewed and approved the final version of the manuscript. D.R.L.: ophthalmologist responsible for patient care; participated in the description of fundoscopy exams and the coordination of article writing since the first version; reviewed and approved the definitive version of the manuscript.

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The NICU Discharge Dilemma: How Leveraging Technology Can Support Care Teams, Empower Families, and Measurably Improve the Discharge Process

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Introduction

The transition from Neonatal Intensive Care Unit (NICU) to home represents a critical juncture in the continuum of care for newborns, their families, and their healthcare providers. This period often termed the "healthcare discharge dilemma," involves a complex set of challenges that includes a patient who is medically ready for discharge and an emotionally prepared family who has demonstrated the knowledge and skills to care for their baby safely at home. While the NICU's highly specialized and supportive environment meets the infant's immediate medical needs, it vastly differs from the home setting, where families must assume full responsibility for the infant's care. To prevent high rates of emergency department visits and readmissions after discharge from the hospital, a family must feel confident in their competence level to care for their baby's specific medical needs. A safe and successful discharge includes a multidisciplinary team approach. Coordinating the busy day-to-day patient caseloads while ensuring clear, consistent communication throughout the NICU stay adds complexity to the process.

Discharge planning varies widely across NICUs, often relying on outdated methods to track critical discharge criteria and milestones. Healthcare staffing shortages and inconsistent patient care providers further complicate the process. This often leads to triangulated and ineffective patient communication among healthcare team members and necessitates reliance on paper-based or less efficient methods to keep the care team aligned and informed. Such practices negatively affect the quality of education the family receives, prolong hospital stays, and delay coordination in follow-up care. Educating families and training them for home care is often compressed into the 48 to 72 hours before discharge, placing substantial pressure on the healthcare workers and leaving families ill-equipped to care for their infants at home safely.[1] These challenges are further intensified by data showing that 43% of NICU parents have low levels of health literacy and that regardless of health literacy levels, parents were unable to retain 80% of care instructions given to them before discharge.[2,3] The challenges are further intensified by a shortage of clinical staff and fragmented communication among healthcare professionals and families,

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which leads to misunderstandings and delays and places the infant's overall well-being at risk.

This paper introduces the common discharge challenges in healthcare and presents survey data on the significant gaps in the current discharge process, utilizing the Jobs to be Done (JTBD) methodology.[4] The need to leverage tecÚology with solutions that support care teams and families with a successful, efficient, and safe transition to home from the NICU will also be reviewed.

Jobs to be Done Methodology

The Jobs to be Done (JTBD) framework is a research and product development methodology that deploys a user-centric approach that shifts the focus from the product's features to a more comprehensive understanding of the individual's needs and what drives their behavior.

Underpinning the JTBD framework is a set of core tenets that collectively build a foundation upon which organizations build a sustainable practice of innovation.[5] By identifying unmet needs, researchers can develop solutions that get the "job" done more accurately and efficiently. Additionally, the framework aids in uncovering more profound insights into the functional, emotional, and social determinants behind the user's preferred choices, behavior, and needs. Utilizing this approach shifts the focus from the product or the customer to the job itself, which remains consistent over time, thus offering a stable target for value-creation efforts.[6]

Table 1. Users Initially Identified in Supporting the Transition from NICU to Home Steps

User Role	Role Description
NICU Nurse	Offers specialized nursing care in the NICU and assists in preparing the family for home care.
Discharge Coordinator	Typically, a NICU nurse specializing in the NICU discharge process and ensuring that all necessary equipment and follow-up appointments are organized for a smooth transition to home care.
Parent/Caregiver	Plays the central role in providing care and ensuring a loving, stable home environment.
Case Manager	Coordinates different aspects of care and ensures smooth communication among all involved parties.
Social Worker	Helps the family navigate healthcare systems and access necessary resources for home care.
Provider/Neonatologist	Oversees the medical care of NICU patients and often in collaboration with a Neonatal Nurse Practitioner, will coordinate and plan the home-care transition.
Respiratory Therapist	Manages respiratory care needs, especially for infants who require home respiratory support.
Neonatal Therapists	
Physical Therapist	Assesses and aids in the infant's physical development and progress.
Occupational Therapist	Focuses on improving the baby's skills for daily activities and overall development.
Speech-Language Pathologist	Assess and follow the infant's oral feeding progression.
Dietitian	Provides nutritional guidance tailored to the infant's specific needs.
Lactation Consultant	Supports breastfeeding success and ensures proper nutrition for the baby.
Pharmacist	Manages and advises on medications the infant needs to continue at home.
Insurance Coordinator	Assists the family with insurance-related issues and coverage for required treatments.
Family Therapist/NICU Psychologist	Supports the family in coping with the emotional and psychological aspects during their NICU stay and as they transition home.
Pediatric Subspecialists	Specialized pediatric providers.
Pediatrician	Provides ongoing medical oversight and care for the infant after discharge from the NICU.
Home Health Nurse	Provides nursing care at home, ensuring continuity of care post-discharge.

The JTBD framework offers a lens through which we can better understand the specific needs and challenges NICU families and care teams face throughout the discharge process. Our team followed the following process:

1. **Identify the JTBD. "**Coordinating the care transition from NICU to home" was the ultimate JTBD that emerged through interviews and surveys with clinicians and caregivers.
2. **Identify the customers.** Sixteen functional roles were identified as directly involved with the job and varied across a continuum of healthcare providers (Table 1).
3. **Narrow focus to a specific market.** More than any other functional role, NICU bedside nurses are the executors of this job. The primary beneficiary of their efforts is the patient's family, often their parents, reinforcing the collaborative approach needed between families and bedside nurses for a successful discharge.
4. **Create and validate the job map.** Ten core job steps (listed below) were identified into a job map, outlining the steps required to accomplish the job.[7] Feedback was received from clinicians on the job map.
5. **Confirm the desired outcomes for each job step.** Outcomes represent the set of metrics that customers use to evaluate the successful completion of any given job step. Once desired outcomes were established, unmet customer needs that stabilized over time were identified, regardless of the products or services used.
6. **Assess the importance and difficulty of each outcome.** Using a questionnaire, each outcome linked to every job step was assessed for its difficulty level and importance to the bedside nurse executing the job.
7. **Synthesize the data.** Analyze the data and employ opportunity scoring to pinpoint unfulfilled customer needs. Organize the results based on scores and illustrate them on an opportunity map.
8. **Identify innovation opportunities that align with our mission.** The team assessed which outcomes aligned with our mission statement, 'Equipping care teams and empowering families of neonatal and pediatric patients to improve outcomes.' and could be influenced by tecÚology and services in a measurable and user-centric approach.

Survey & Analysis

A comprehensive questionnaire was developed to gain insight into the needs of bedside nurses when coordinating the care transition from the NICU to home. The opportunity to participate in the survey was posted on several social media groups for NICU nurses. All participants were required to practice actively as neonatal nurses in the United States. Respondents who provided complete data were awarded a $50 Amazon e-gift card for their participation. They were instructed to base their survey responses on the last NICU they worked in if they had experience in multiple institutions. Each respondent was asked to rank the level of difficulty and importance of outcomes corresponding to the ten job steps on a 5-point Likert scale. The job steps included:

1. **Formulate a Detailed Care Plan.** The ability to develop a comprehensive care plan tailored to the newborn's specific health needs and their parent/caregiver's unique needs.
2. **Engage with Family and Caregivers.** The ability to effectively communicate with the newborn's family, providing updates and involving them in the care process.
3. **Collaborate with NICU Team.** The ability to work closely with a multidisciplinary team, including doctors and therapists, to ensure integrated care for the newborn.

Table 2. Average Opportunity Score Across the Ten Job Steps

Job Step	Average Opportunity Score
Educate Family for Home Care – The ability to prepare the family for the newborn's care post-discharge, including training in special care techniques and medication management.	**11.9**
Engage with Family and Caregivers – The ability to effectively communicate with the newborn's family, providing updates and involving them in the care process.	**11.6**
Collaborate with NICU Team – The ability to work closely with a multidisciplinary team, including doctors and therapists, to ensure integrated care for the newborn.	**11.4**
Coordinate Post-NICU Care – The ability to organize follow-up medical care and support services for after the newborn leaves the NICU.	**10.9**
Provide Post-Discharge Support – The ability to offer follow-up support and resources to the family, ensuring ongoing care and addressing any post-discharge challenges.	**10.7**
Implement Discharge Plan – The ability to oversee the execution of the discharge plan, ensuring a smooth transition from the NICU to home.	**10.4**
Formulate a Detailed Care Plan – The ability to develop a comprehensive care plan tailored to the newborn's specific health needs and their parent/caregiver's unique needs.	**10.3**
Monitor Patient's Progress – The ability to continuously observe and record the patient's health status, responding to changes and adjusting care as necessary during their stay in the NICU.	**10.3**
Adjust Care Plan Based on Patient's Response – The ability to modify the care strategy in response to the patient's progress and new medical information, ensuring the most effective treatment approach.	**10.1**
Prepare for Discharge – The ability to manage all aspects of the newborn's discharge process, including documentation and logistics, in the days leading up to discharge.	**9.7**

4. **Monitor Patient's Progress.** The ability to continuously observe and record the patient's health status, responding to changes and adjusting care as necessary during their stay in the NICU.
5. **Adjust Care Plan Based on Patient's Response.** The ability to modify the care strategy in response to the patient's progress and new medical information, ensuring the most effective treatment approach.
6. **Educate Family for Home Care.** The ability to prepare the family for the newborn's care post-discharge, including training in special care tecÚiques and medication management.
7. **Coordinate Post-NICU Care.** The ability to organize follow-up medical care and support services after the newborn leaves the NICU.
8. **Prepare for Discharge.** The ability to manage all aspects of the newborn's discharge process, including documentation and logistics, in the days leading up to discharge.
9. **Implement Discharge Plan.** The ability to oversee the execution of the discharge plan, ensuring a smooth transition from the NICU to home.
10. **Provide Post-Discharge Support.** The ability to offer follow-up support and resources to the family, ensuring ongoing care and addressing any post-discharge challenges.

The nurses ranked the difficulty level and importance of 130 outcomes across the ten job steps. Traditionally, responses are analyzed utilizing opportunity scoring, a method designed to analyze the gap between the importance of associated customer outcomes and their satisfaction with the current solution.

Our team surveyed on 'difficulty' instead of 'satisfaction' to keep the survey context agnostic of existing products and solutions. For the purposes of opportunity scoring, difficulty values were set to correlate to satisfaction: "Very Difficult" was assigned a value of 1 (i.e., Very Dissatisfied), "Very Easy" was assigned a value of 5 (i.e., Very Satisfied), and so on.

The percentage of respondents who responded with a 4 or 5 was computed for each outcome. For example, if 90% of the respondents rate an outcome a 4 or 5 for importance, the Importance value entered into the algorithm is 9.0, and if 30% of the respondents rate an outcome a 4 or a 5 for satisfaction, the satisfaction value entered into the algorithm is a 3.0. The formula below was then used to determine the opportunity score:

Market Opportunity =
Importance + max (0, Importance – Satisfaction)

Finally, the outcome scores were graphed on an opportunity landscape (Figure 1).

Figure 1. Opportunity Landscape: Bedside Nurses Coordinating the Care Transition from NICU to Home

Survey Results

A total of 100 US-based, practicing NICU nurses responded to the survey, 64 of whom completed it. The nurses represented 33 states and level II-IV NICUs across rural, urban, and academic settings. Across all job steps, the average computed scores for each measurement were 8.3 (importance), 5.8 (satisfaction), and 10.7 (opportunity).

Table 3. Top 10 Outcomes Directly Connected with AngelEye Health's Mission

Rank	Outcome	Importance	Satisfaction	OppScore
1	Ascertain that the family is prepared for the long-term care requirements, e.g., chronic condition management, ongoing therapies, etc.	9.38	3.13	15.63
2	Confirm the family's understanding of long-term care requirements for chronic conditions, e.g., medication management, therapy continuation, etc.	9.38	4.53	14.23
4	Determine the family's understanding of the baby's medical condition, e.g., diagnosis, prognosis, etc.	9.38	5.47	13.29
5	Determine the family's ability to recognize signs of illness or distress in the baby, e.g., fever, unusual crying, etc.	9.69	6.25	13.13
9	Determine the family's preparedness for managing potential health complications, e.g., allergic reactions, respiratory issues, etc.	9.22	5.63	12.81
10	Ascertain the family's readiness to handle the emotional aspects of caring for a baby from the NICU, e.g., anxiety management, emotional support, etc.	8.75	4.84	12.66
11	Know that the family is informed about the signs of normal versus concerning behavior in the baby, e.g., sleep patterns, feeding habits, etc.	9.84	7.03	12.65
12	Avoid overwhelming the family with too much technical information, focusing on practical and essential care aspects.	8.13	3.75	12.51
14	Confirm the arrangement of regular follow-up appointments with healthcare providers, e.g., pediatric check-ups, therapy sessions, etc.	9.22	5.94	12.5
15	Avoid any lapses in the baby's care during the transition from hospital to home, ensuring a smooth and continuous care plan.	9.06	5.63	12.49

Nine of the ten job steps had average opportunity scores > 10, reflecting a vastly underserved market. The job step 'Educate Family for Home Care' had the highest opportunity score of 11.9, followed by 'Engage with Family and Caregivers' at 11.6 and 'Collaborate with NICU Team' at 11.4 (**Table 2**).

The opportunity score of 101 of the 130 outcomes was in the 'underserved' category. Two of the 130 were 'overserved,' and the remaining 27 were 'appropriately served.' These results underscore the significant unmet needs faced by bedside nurses in the NICU when coordinating discharge. (**Figure 1**)

Twenty-four of the 130 outcomes had an opportunity score >12, representing a 'high opportunity.' The outcome with the highest opportunity score was 'Ascertain that the family is prepared for the long-term care requirements," followed by 'Confirm the family's understanding of long-term care requirements for chronic conditions.' **(Table 3).**

The Role of Technology in Addressing the Discharge Dilemma

This research identifies numerous underserved needs of NICU nurses that are crucial to the successful transition of care from NICU to home. Seventy percent of those underserved needs were correlated with the job steps 'Educate Family for Home Care,' 'Engage with Family and Caregivers,' and 'Coordinate Post-NICU care.' Targeted interventions in the research setting have positively impacted the discharge process, including the ability to reduce the length of stay. However, these solutions have yet to be incorporated into clinical practice in a sustained and scalable manner. Better developed tools are needed for nurses to successfully prepare families for the safe transition from NICU to home.

Advancements in healthcare tecÚology present a unique opportunity to address the discharge dilemma in the NICU. Digital platforms can help bridge the gap between the hospital and home, providing families access to educational resources, care plans, and direct communication with healthcare providers.

For care teams, tecÚology can streamline the discharge processes, improve communication, optimize clinical time and resources, reduce administrative burdens, and facilitate more success in post-discharge care. Foundational needs that tecÚology can positively impact include:

1. **Surveys:** By utilizing targeted surveys, education and support are tailored to each family's needs, enhancing the clinicians' ability to offer personalized care. This strategy improves patient outcomes and family satisfaction.
2. **Education and Resource Delivery:** We equip families with easily accessible essential education and resources relevant to their baby's health and transition to home, increasing their confidence and readiness for discharge.
3. **Flexible Scheduling:** Our coordination system enhances care team collaboration and family involvement, streamlines care activities, and improves neonatal health outcomes.
4. **Integrated Communications:** Our communication system ensures families are informed and engaged throughout the NICU stay, enhancing the care experience and supporting positive patient outcomes.
5. **NICU Roadmap:** A dynamic visual roadmap integrates care and communication between all stakeholders, offering customized guidance for families and care teams, facilitating smoother transitions from NICU to home and better overall long-term neonatal health.

Conclusion

Transitioning from the NICU to home is a pivotal moment for infants and their families, marked by significant challenges that necessitate comprehensive support from all healthcare team members. Embracing tecÚological solutions can transform the discharge process into a more manageable, less stressful, and empowering family experience while optimizing the efficiency and effectiveness of care teams. Moving forward, healthcare innovators and leaders must prioritize developing and implementing tecÚologies that provide the care team members with the tools they need to safely and effectively help families transition from NICU to home.

AngelEye Health is developing the first evidence-based NICU navigation and discharge coordination software that leverages the power of your EHR and cultivates confident families. This new solution can improve staff efficiency, save staff time, and proactively identify and support at-risk families to improve long-term health outcomes. Furthermore, it represents additional steps to a more integrated, family-centered approach essential for successful outcomes and advances AngelEye's goal and mission. With the help of tecÚology to support the individual jobs required by each stakeholder involved in the transition from NICU to home, we can create the pathway for a more supportive, efficient, and, most importantly, safe discharge for our patients and their families. Visit AngelEyeHealth.com to learn more.

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Risk Factors for Preterm Birth: An Umbrella Review of Meta-Analyses of Observational Studies

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Abstract

Background. Preterm birth defined as delivery before 37 gestational weeks is a leading cause of neonatal and infant morbidity and mortality. The aim of this study is to summarize the evidence from meta-analyses of observational studies on risk factors associated with PTB, evaluate whether there are indications of biases in this literature, and identify which of the previously reported associations are supported by robust evidence.

Methods. We searched PubMed and Scopus until February 2021, in order to identify meta-analyses examining associations between risk factors and PTB. For each meta-analysis, we estimated the summary effect size, the 95% confidence interval, the 95% prediction interval, the between-study heterogeneity, evidence of small-study effects, and evidence of excess-significance bias. Evidence was graded as robust, highly suggestive, suggestive, and weak.

Results. Eighty-five eligible meta-analyses were identified, which included 1480 primary studies providing data on 166 associations, covering a wide range of comorbid diseases, obstetric and medical history, drugs, exposure to environmental agents, infections, and vaccines. Ninety-nine (59.3%) associations were significant at $P < 0.05$, while 41 (24.7%) were significant at $P < 10^{-6}$. Ninety-one (54.8%) associations had large or very large heterogeneity. Evidence for small-study effects and excess significance bias was found in 37 (22.3%) and 12 (7.2%) associations, respectively. We evaluated all associations according to prespecified criteria. Seven risk factors provided robust evidence: amphetamine exposure, isolated single umbilical artery, maternal personality disorder, sleep-disordered breathing (SDB), prior induced termination of pregnancy with vacuum aspiration (I-TOP with VA), low gestational weight gain (GWG), and interpregnancy interval (IPI) following miscarriage < 6 months.

Conclusions. The results from the synthesis of observational studies suggest that seven risk factors for PTB are supported by robust evidence. Routine screening for sleep quality and mental health is currently lacking from prenatal visits and should be introduced. This assessment can promote the development and training of prediction models using robust risk factors that could improve risk stratification and guide cost-effective preventive strategies.

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Background

Preterm birth (PTB) is defined as delivery before 37 gestational weeks and is a leading cause of infant morbidity and mortality.[1-4] It is estimated that 15 million babies are born preterm annually and the PTB rate ranges between 5 and 18% worldwide.[3] Specifically, the prevalence of PTB varies by geographic location ranging from 12 to 13% in the USA[1,2] and from 5 to 9% in Europe.[2] Advances in neonatology and the administration of corticosteroids before birth have significantly improved the prognosis of babies born preterm.[5] Even though vigorous research was carried out over the last 40 years, which costed millions of dollars and focused on the prediction and prevention of preterm birth its incidence remains relatively unchanged.[5] The most probable explanation is that preterm birth is a syndrome, and many different causes may act synergistically to its manifestation.[5]

Numerous systematic reviews and meta-analyses have assessed various, non-genetic risk factors of preterm labor. Several environmental and clinical parameters such as present pregnancy characteristics, previous pregnancy history,[4]

infections,[6,7] environmental exposures, pharmaceutical factors,[8] and surgical interventions have been proposed as plausible factors related to PTB.[9] To date, there is no assessment of the epidemiological quality of this literature. Identifying robust risk factors for PTB should help us define a study population for specific interventions, allocate available resources effectively, allow for risk-specific treatment, and understand the mechanisms leading to PTB.[1]

To our knowledge, there is no previous effort to summarize existing evidence of meta-analyses of non-genetic risk factors for PTB. We conducted an umbrella review across published meta-analyses of observational studies, including topics related to a wide range of risk factors including obstetric history, medical history, drugs, socioeconomic status indicators, and environmental and dietary risk factors, with the goal of mapping the existing evidence and critically evaluating the reported associations. We applied stringent criteria to assess potential systematic biases.

Methods

We conducted an umbrella review which is a comprehensive and systematic approach that collects and critically evaluates all systematic reviews and meta-analyses performed on a specific research topic.[10] We used previously described, standardized methods that have been already used in published umbrella reviews referring to risk factors related to various outcomes[11-14] and have been elaborated below.

A protocol for this umbrella review was registered in the International prospective register of systematic reviews (PROSPERO 2021 CRD42021227296).

Search strategy

Two researchers (A.E., I.M.) independently searched PubMed and Scopus databases from inception to February 2021, to identify systematic reviews with meta-analyses of studies that examine the association between risk factors and preterm birth. The search strategy included combinations of the Medical Subject Headings (MESH) terms, keywords, and word variants for terms "preterm birth" AND ("systematic review" OR "meta-analysis"). Titles and abstracts were screened, and potentially eligible articles were retrieved for full-text evaluation. A detailed description of our search strategy is provided in Additional file 1.

Eligibility criteria and data extraction

We included systematic reviews with meta-analyses investigating the association between various types of exposures as risk factors for PTB. Specifically, we included studies with singleton pregnancies and studies where PTB was evaluated as the primary outcome. Case reports or series and individual participant data meta-analyses were excluded. We also excluded studies that set time limits on time span or were performed on a restricted setting (i.e., conducted for one specific country). Studies that assessed PTB as a secondary outcome were also excluded. We excluded meta-analyses that assessed PTB as a secondary outcome for two reasons; first, in any analysis of a secondary outcome, there is a possibility of lack of power to detect an effect, given that studies design their power calculations based on a primary outcome. Therefore, any assessment of effect size, heterogeneity, and other statistics would be meaningless under the lack of power. Second, some components of the grading of evidence, such as publication bias, are assessed based on the primary outcome of the studies and could not be evaluated for secondary outcomes. Furthermore, we excluded studies including multiple pregnancies and studies that assessed genetic or over -omics features as risk factor for PTB. All studies were compared to avoid the possibility of duplicate or overlapping samples. If more than one meta-analysis referring to the same research question was eligible, parameters such as the largest amount of component studies with data on individual studies' effect sizes, publication year, and in some cases the number of participants on individual studies were considered to retain the appropriate one for the main analysis.

Publications whom estimates of the studied associations, such as relative risks (RR) and 95% confidence intervals (CIs) were not reported or could not be retrieved/calculated were excluded from the analysis. For the non-environmental risk factors, we also excluded meta-analyses that did not provide the number of cases in the exposed and non-exposed groups, which is used for the calculation of the excess significance test. For the environmental risk factors, since most commonly they report the results as per unit(s) increase in exposure and the entire population is exposed, we included them even if they did not report the number of cases and total sample size. As most of the included meta-analyses did not report the number of cases or the sample size of the studies included, we were unable to estimate the power of each meta-analysis and the excess significance test.

Eligible articles were screened by four independent reviewers (AE/IM and EB/TK). Any disagreement between reviewers was resolved by consensus or after the evaluation of a third author (SP or EE). The data of eligible studies were extracted in a predefined data extraction form recording for each study the first author, journal, year of publication, the examined risk factors, and the number of reviewed studies. Either the study-specific relative risk estimates (risk ratio, odds ratio, hazard ratio, incidence rate ratio) and the confidence intervals were extracted or the mean and the standard deviation for continuous outcomes were also noted in this form. We also extracted the exposed and control groups used, outcome assessed, study population, exposure characteristics, number of studies in the meta-analysis, metaanalysis metric and method, effect estimate with the corresponding 95% confidence interval, number of cases and total sample size, I^2 metric and the corresponding χ^2 *P*-value for the *Q* test, and Egger's regression *P*-value.

Assessment of summary effect and heterogeneity

We re-calculated summary effects and 95% confidence intervals (CIs) for each meta-analysis via fixed and random effects model.[15,16] 95% prediction intervals (PI) were also computed for the summary random-effects estimates, which further account for between-study heterogeneity indicating the uncertainty for the effect that would be expected in a new study examining the same association.[17,18] A PI describes the variability of the individual study estimates around the summary effect size and represents the range in which the effect estimate of a new study is expected to lie.

The largest study was considered to be the most precise if there was a difference between the point estimate and the upper or lower 95% confidence interval less than 0.20.[19] If the largest study presented a statistically significant effect, then we recorded this as a part of the grading criteria.

Between-study heterogeneity was assessed and *P*-value of the χ^2-based Cochran Q test and the I^2 metric for inconsistency

(reflecting either diversity or bias) was reported, too. I^2 metric was used to indicate the ratio of between-study variance over the sum of within- and between-study variances, ranging from 0 to 100%.[20] Values exceeding 50% or 75% are usually considered to represent large or very large heterogeneity, respectively.[21] 95% confidence intervals were calculated as per Ioannidis et al.[21]

Assessment of small-study effects

Small studies tend to give substantially larger estimates of effect size when compared to larger studies. We evaluated the evidence of the presence of the small-study effects, to identify publication and other selective reporting biases. They can also reflect genuine heterogeneity, chance, or other reasons for differences between small and large studies.[22] We evaluated whether smaller (less precise) studies lead to inflated effect estimates compared to larger studies. We used the regression asymmetry test proposed by Egger, which examines the potential existence of small-study effects via funnel plot asymmetry.[23] Egger's test fits a linear regression of the study estimates on their standard errors weighted by their inverse variance. Indication of small-study effects based on Egger's asymmetry test was claimed when P-value ≤ 0.10. This is considered as an indication of publication bias; indication of small-study effects based on Egger's asymmetry test was claimed when P-value ≤ 0.10 and the random effects summary estimate was larger compared to the point estimate of the largest (most precise) study in the meta-analysis.

Excess statistical significance evaluation

The excess significant test was applied to evaluate the existence of a relative excess of significant findings in the published literature for any reason (e.g., publication bias, selective reporting of outcomes or analyses).[24] This is a binomial test evaluating whether the number of positive studies in a meta-analysis was too large according to the power that these studies have to detect plausible effects at $\alpha = 0.05$. The power of each component study was calculated using the fixed-effects summary, the random effects summary, or the effect size of the largest study (smallest SE) as the plausible effect size[13] using an algorithm using non-central t distribution to calculate the power of each study.[25] Excess statistical significance for single meta-analyses was claimed at $P < 0.10$ (one-sided $P < 0.05$, with observed > expected as previously proposed), given the power to detect a specific excess will be low, especially with few positive studies.[24]

Grading of evidence

We followed a 4-level grading (robust, highly suggestive, suggestive, and weak) to evaluate the strength of the evidence based on the following criteria: number of cases, summary random-effects P-value, between-studies heterogeneity, 95% PI, small-study effects bias, and excess statistical significance.[26] This grading approach based on these parameters was used because it allows for an objective, standardized classification of the level of evidence and has been previously shown to provide consistent results with other more subjective grading schemes.[26-30]

Briefly, meta-analyses were considered to be supported by robust evidence if the association was supported by more than 1000 cases, a highly significant association (the random effects model had a P-value ≤ 10^{-6}, a threshold that is considered to substantially reduce false positive findings),[31-33] there was absence of high heterogeneity based on $I^2 < 50\%$, the 95% PI excluded the null value, and there was no evidence of small-study effects or excess statistical significance. Highly suggestive evidence required more than 1000 cases, a highly significant association (a random-effects P-value ≤ 10^{-6}), and the largest study in the meta-analysis was significant at $P < 0.05$. Associations based on meta-analyses with a random-effects P-value ≤ 10^{-3} and included more than 1000 cases[31-33] were graded as suggestive evidence. The remaining significant associations at $P < 0.05$ were graded as weak evidence. We need to highlight that this specific grading scheme focuses on the reduction of false-positive findings and the evaluation of potential biases in the studied associations. Therefore, the set of criteria used here is not ideal for a detailed evaluation of non-significant associations and to distinguish insufficient evidence from robust evidence of no association. That would require a different approach and another set of criteria altogether that would focus on the power of the meta-analyses to observe a significant effect, which was beyond the scope of our review. This grading system has been evaluated[34] and showed that these criteria may offer relatively independent and complimentary insights into the evidence of an observational association. Other systems such as GRADE[35] and ROBIS[36] have focused mainly on evaluating randomized evidence from RCTs or non-randomized studies of intervention. Statistical analyses were performed using STATA version 14 (StataCorp, TX, USA).

Results

Description of eligible meta-analyses

The search identified 2985 items, of which 2420 were excluded after a review of the title and abstract (Figure 1, PRISMA flowchart). Of the remaining 565 articles that were reviewed in full text, eight articles did not report the appropriate information for the calculation of excess of statistical significance (either because the total sample size was missing or the study-specific relative risk estimates were missing), and 134 articles were excluded because a larger systematic review or meta-analysis investigating the same risk factor was available. From the 219 comparisons, we further excluded the ones that included one or two studies (53 comparisons). Therefore, 218 articles were analyzed, of which 133 were systematic reviews without any quantitative component and 84 were meta-analyses. The 84 eligible meta-analyses[4,6-9,37-115] included data on 166 comparisons and 1480 primary studies.

Summary effect sizes and significant findings

Three to 152 studies, with a median of 11 studies, were included per meta-analysis. The median number of cases and total population in each study were 91 and 1004, respectively. The median number of cases and total population in each meta-analysis was 7266 and 94,907, respectively. The number of cases was greater than 1000 in 94 comparisons. Overall, 570 (38,5%) individual studies observed statistically significant results at $P < 0.05$. Thirty-nine meta-analyses used the Newcastle-Ottawa scale to assess qualitatively the included primary studies. One meta-analysis used assessment criteria for non-randomized observational studies adapted from Duckitt and Harrington, 3 meta-analyses used the Methodological Index for Non-Randomized Studies (MINORS), and 37 meta-analyses used other assessment tools. Four meta-analyses did not perform any quality assessment. Details of the 166 comparisons that included 1480 individual study estimates are summarized in Additional file 2.

Of the 166 comparisons, 99 (59.3%) had statistically significant findings at $P < 0.05$ using the random-effects model, of which 93

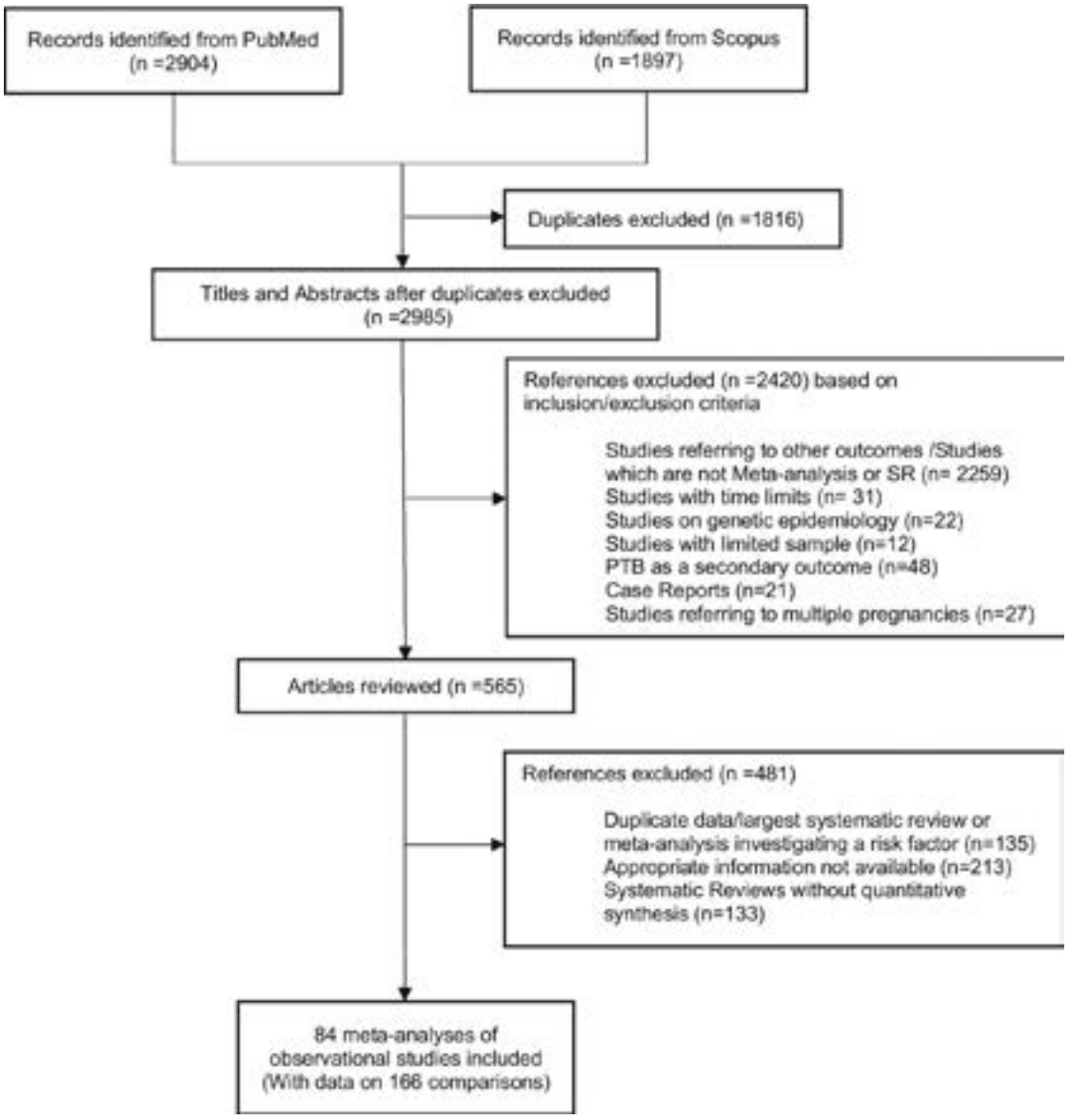

Figure 1. Flow diagram for the selection of included studies.

reported an increased risk and six a decreased risk for preterm birth. The associations identified to decrease the risk of PTB are the following: preconception care vs no care,[47] magnesium supplementation vs placebo,[72] single vs double embryo transfer,[87] high gestational weight gain vs normal gestational weight gain,[106] interpregnancy interval following miscarriage < 6 months vs > 6 months,[108] and greenery including only a 100-m normalized difference vegetation index (NDVI) buffer.[113] Of these, a total of 61 (36.8%) associations presented statistically significant effect at $P < 0.001$, while only 41 (24.7%) remained significant after the application of a more stringent *P*-value threshold of $P < 10^{-6}$ (Table 1).

Between-study heterogeneity and prediction intervals

Forty-four (26.5%) comparisons had large ($I^2 \geq 50\%$ and $\leq 75\%$) and 47 comparisons (28.3%) had very large ($I^2 > 75\%$) heterogeneity estimates (see Additional file 2). When calculating the 95% PIs, the null value was excluded in only thirty-one (18.7%) comparisons.

Small-study effects

Evidence for statistically significant small-study effects (Egger test $P < 0.10$ and random-effects summary estimate larger compared with the point estimate of the largest study in the meta-analysis) was identified in 37 (22.3%) comparisons (see Additional file 2).

Test of excess statistical significance

Evidence of excess-statistical-significance bias was observed in 12 (7.2%) associations, with statistically significant ($P < 0.05$) excess of positive studies under any of the three assumptions for the plausible effect size, i.e., the fixed-effects summary, random-effects summary or

Grading of evidence

The summary of the epidemiological credibility for 166 associations of risk factors for PTB is shown in Additional file 2. Seven of the 166 associations (4.2%) were supported by robust evidence (amphetamines, fetus with isolated single umbilical artery, maternal personality disorder, sleep-disordered breathing (SDB), prior induced termination of pregnancy (I-TOP) with vacuum aspiration (VA), low gestational weight gain, and interpregnancy interval (IPI) following miscarriage less than

Table 1. Assessment across the statistically significant associations for preterm birth.

Level of evidence	Criteria
Robust	> 1000 cases, [a] $P < 10^{-6}$, not large heterogeneity (I^2 < 50%), 95% prediction interval excluding the null value, no evidence for small-study effects[b], and excess significance bias [c]
Risk factors supported by robust evidence	Amphetamines[53] Isolated single umbilical artery[60] Maternal personality disorder[70] SDB (objective assessment)[80] Prior I-TOP with VA[98] Low GWG[107] IPI following miscarriage of < 6 m (compared to IPI following miscarriage of ≥ 6 months, with Conde-Agudelo A, 2004 excluded)[108]
Highly Suggestive	> 1000 cases, [a] $P < 10^{-6}$ and statistically significant effect present at the largest study at $P < 0.05$
	Risk factors supported by highly suggestive evidence 1st trimester bleeding[51] Prior surgical I-TOP (for PTB in singleton pregnancies)[98] Obstetric cholestasis[66] PCOS[115] Cancer survivors[41] Placenta previa[43] African/Black race[49] Aboriginal ethnicity[50] BMI of > 40 kg/m^2 (compared to BMI = 30-34.9 kg/m^2)[75] BMI of > 40 kg/m^2 (compared to BMI = 30-39.9 kg/m^2)[75] Endometriosis (combined spontaneous conception and assisted reproduction)[8] Endometriosis (spontaneous conception)[8] Maternal age of ≥ 45 years old[103] CKD during pregnancy[104] Underweight women[105] Maternal vitamin D status (for spontaneous PTB)[110] SMM: hemorrhagic disorders[68] SMM: hepatic disorders[68] LEEP[111] LLETZ for CIN[112] Any type of treatment for CIN with a cone depth of ≥ 10-12 mm (compared to untreated CIN)[112] Any type of treatment for CIN with a cone depth of ≥ 15-17 mm (compared to untreated CIN)[112] Intimate partner violence[39] Unmarried women[52] Cocaine[79] Entire pregnancy high level $PM_{2.5}$ exposure[48]
Suggestive	> 1000 cases, [a] $P < 10^{-3}$
Risk factors supported by suggestive evidence	Pre-gravid OC use[40] Marijuana during pregnancy[57] SMM: thromboembolic disorders[68] Periodontal disease[74] Women of short stature[77] Antipsychotics during pregnancy[38] *Trichomonas vaginalis* infection[84] Blastocyst-stage embryo transfer (vs cleavage embryo transfer)[86] Fresh blastocyst transfer (for PTB)[89] Fresh blastocyst transfer (for very PTB < 32 weeks)[89] HPV Infection (crude)[7] HPV Infection (age adjusted)[7] > 1 prior surgical I-TOP[98] Any type of treatment for CIN with a cone depth of ≥ 20 mm (compared to untreated CIN)[112] Greenery (including only a 100-m NDVI buffer)[113]
Weak	The rest associations with [a] $P < 0.05$
Risk factors supported by weak evidence	History of preterm twins[4] History of preterm twins 34-36 + 6 weeks[4] History of preterm twins 30-33 + 6 weeks[4] History of preterm twins < 30 weeks[4] History of spontaneous twin preterm birth[4] History of spontaneous twin preterm birth 34-36 + 6 weeks[4] Subseptate uterus[46] Cancer survivors treated after radiotherapy[41] H1 Antihistamine[37] Velamentous cord insertion[42] Metformin[44] Diabetic nephropathy in T1DM[45]

Level of evidence	Criteria
	Preconception care[47]
	Asian race[49]
	Hispanic ethnicity[49]
	Laparoscopic appendectomy[9]
	Hyperemesis gravidarum (cohort studies)[54]
	Hyperemesis gravidarum (case control studies)[54]
	Arcuate uterus[46]
	Septate uterus[46]
	Bicornuate uterus[46]
	Didelphys uterus[46]
	Unicornuate uterus[46]
	Triptan[55]
	Migraine[55]
	Topical retinoids (exposed infants)[56]
	Hydroxychloroquine[56]
	TB[58]
	Multivitamins[59]
	Fetus with small thymus[61]
	Probiotics during pregnancy (for PTB < 34 weeks)[62]
	Probiotics during pregnancy (for PTB < 37 weeks)[62]
	Home visits for pregnant women[63]
	APS[64]
	Bed Rest (in developing regions, for PTB < 37 weeks)[65]
	Bed Rest (in developed regions, for PTB < 37 weeks)[65]
	Bed Rest (in developing regions, for very PTB)[65]
	Bed Rest (in developed regions, for very PTB)[65]
	Pregnancy-associated malaria[67]
	Nicotine Replacement Therapy[69]
	Women involved in motor vehicle crashes[71]
	Magnesium supplementation[72]
	Donor sperm (for PTB)[73]
	Donor sperm (for very PTB)[73] Bariatric surgery[76]
	Vitamin C and others supplementation[78]
	SDB (questionnaire-based assessment)[80]
	Asthma with exacerbation during pregnancy[81]
	Asthma without exacerbation during pregnancy[81]
	Alcohol consumption before or during pregnancy[83]
	Vaginal clindamycin treatment for bacterial vaginosis[85]
	Single embryo transfer (randomized clinical trials)[87]
	Single embryo transfer (cohort studies)[87]
	Stimulated cycle IVF[88]
	Bacterial vaginosis[90]
	Intermediate vaginal flora[90]
	HPV 6/11/16/18 vaccine in periconceptional period or during pregnancy[6]
	Quinolones during 1st trimester[91]
	Macrolides[92]
	Clindamycin[92]
	Metronidazole alone or in combination[92]
	Metronidazole[92]
	Dental caries[93]
	Celiac disease[94]
	Single-twin death after 14 weeks of monochorionic pregnancy[95]
	Prenatal care (observational studies)[96]
	Prenatal care (randomized clinical trials)[96]
	Endometriosis (assisted reproduction)[8]
	Knowledge of TVU-measured CL in singletons pregnancies with symptoms of PTL[97]
	Only 1 prior surgical I-TOP[98]
	Prior 1st trimester surgical I-TOP[98]
	Prior S-TOP[98]
	Prior uterine evacuation[98]
	Prior I-TOP[98]
	Prior I-TOP with dilation and evacuation[98]
	Hyperthyroidism[99]
	Clinical hypothyroidism[100]
	Subclinical hypothyroidism[100]
	Hypothyroxinemia[100]
	LT4 treatment in euthyroid women with thyroid autoimmunity (with Negro R, 2016 included)[101]
	LT4 treatment in euthyroid women with thyroid autoimmunity (with Negro R, 2016 excluded)[101]

Level of evidence	Criteria
	Primiparous mother[102] High GWG[106] IPI following miscarriage of < 6 months (compared to IPI following miscarriage of ≥ 6 months, with Conde-Agudelo A, 2004 included)[108] IPI following miscarriage < 6 months (compared to IPI following miscarriage of 6-12 months)[108] IPI following miscarriage < 6 months (compared to IPI following miscarriage of > 12 months)[108] Treated CIN (for PTB < 37 weeks)[109] Treated CIN during pregnancy[109] Treated CIN before pregnancy[109] Untreated CIN[109] Treated CIN (for spontaneous PTB < 37 weeks)[109] Treated CIN (for PTB < 32 weeks)[109] maternal 25-OHD concentration of < 50 nmol/L[110] maternal 25-OHD concentration of < 75 nmol/L[110] Vitamin D supplementation[110] Maternal Vitamin D status (for PTB in general)[110] Any type of treatment for CIN with a cone depth of ≤ 10-12 mm (compared to untreated CIN)[112] Any type of treatment for CIN with a cone depth of ≥ 10-12 mm (compared to any type of treatment for CIN with a cone depth of ≤ 10-12 mm)[112] Any type of treatment for CIN with a cone depth of ≥ 15-17 mm (compared to any type of treatment for CIN with a cone depth of ≤ 15-17 mm)[112] Any type of treatment for CIN with a cone depth of ≥ 20 mm (compared to any type of treatment for CIN with a cone depth of ≤ 20 mm)[112] 1st trimester $PM_{2.5}$ exposure[48] Entire pregnancy $PM_{2.5}$ exposure[48] 1st trimester high-level $PM_{2.5}$ exposure[48] 1st trimester low level $PM_{2.5}$ exposure[48] Entire pregnancy low level $PM_{2.5}$ exposure[48] Entire pregnancy $PM_{2.5}$ exposure[114] 1st trimester $PM_{2.5}$ exposure[114] 2nd trimester $PM_{2.5}$ exposure[114] 3rd trimester $PM_{2.5}$ exposure[114] 1st month $PM_{2.5}$ exposure[114] Within 1 month before birth $PM_{2.5}$ exposure[114] Individual-level $PM_{2.5}$ exposure[114] Semi-individual-level $PM_{2.5}$ exposure[114] Regional-level $PM_{2.5}$[114] $PM_{2.5}$ exposure[114] 1st trimester NO_2 exposure[82] 2nd trimester NO_2 exposure[82] 3rd trimester NO_2 exposure[82] Whole pregnancy NO_2 exposure[82]

Abbreviations: I-TOP Induced termination of pregnancy, *S-TOP*, Spontaneous termination of pregnancy, *TOP* Termination of pregnancy, *PCOS* Polycystic ovary syndrome, *APS* Antiphospholipid syndrome, *GWG* Gestational weight gain, *T1DM* Type 1 diabetes mellitus, *SDB* Sleep-disordered breathing, *SMM* Severe maternal morbidity, *BMI* Body mass index, *NRT* Nicotine replacement therapy, *TVU* Transvaginal ultrasound, *CL* Cervical length, *PTL* Preterm labor, *CKD* Chronic kidney disease, *IPI* Interpregnancy interval, *CIN* Cervical intraepithelial neoplasia, *25-OHD* 25-hydroxyvitamin D, *LEEP* Loop electrosurgical excision procedure, *LLETZ* Large loop excision of transformation zone, *OC* Oral contraceptive, *LT4* Levothyroxine, *HPV* Human papillomavirus, *TB* Tuberculosis, *IVF* In vitro fertilization, $PM_{2.5}$ Particulate matter with aerodynamic diameter less than or equal to 2.5 μm; PM_{10} Particulate matter with aerodynamic diameter less than or equal to 10 μm, NO_2 Nitrogen dioxide

[a] *P* indicates the *P*-values of the meta-analysis random effects model

[b] Small-study effect is based on the *P*-value from Egger's regression asymmetry test ($P < 0.10$)

[c] Based on the *P*-value ($P < 0.05$) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size results of the largest study (see Additional file 2). In addition, the observed and expected number of positive studies showed that, overall, the excess of positive results was driven by meta-analyses with large estimates of heterogeneity ($I^2 > 50\%$).

6 months) (see Additional file 3). Twenty-six associations (15.7%) were supported by highly suggestive evidence referring to obstetric history, medical history, social and economic profile, and drugs (see Table 1). Fifteen associations (9%) were supported by suggestive evidence, including pre-gravid oral contraceptive use, marijuana, severe maternal morbidity (SMM), periodontal disease, women of short stature, antipsychotics during pregnancy, *Trichomonas vaginalis* infection, blastocyst-stage embryo transfer (vs cleavage stage embryo-transfer), fresh blastocyst transfer (for PTB), fresh blastocyst transfer (for very PTB), HPV infection (crude), HPV infection (age-adjusted), > 1 prior surgical I-TOP, any type of treatment for cervical intraepithelial neoplasia (CIN) with a cone depth ≥ 20 mm (compared to untreated CIN), and greenery.

Regarding the environmental risk factors, higher residential greenness did not tecÚically qualify to be categorized as robust evidence because the random effects *P*-value was 3.25×10^{-6} but fulfilled all other criteria. The rest of the associations regarding different levels of exposure to air pollutants [particulate matter

with aerodynamic diameter less than or equal to 2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2)] in all windows of exposure were classified as weak.

Discussion

In this umbrella review, we evaluated the current evidence, derived from meta-analyses of observational studies on the association between various risk factors and PTB. Overall, from the 166 associations that have been examined, only 4.2% had epidemiologically robust results with no suggestion of bias, as can be inferred by substantial heterogeneity between studies, small-study effects, and excess significance bias. Seven risk factors were supported by robust evidence, including amphetamine exposure,[53] isolated single umbilical artery,[60] maternal personality disorder,[70] sleep-disordered breathing measured with objective assessment,[80] prior induced termination of pregnancy with vacuum aspiration compared to no termination,[98] low gestational weight gain compared to normal weight gain,[107] and interpregnancy interval following miscarriage less than 6 months compared to more than 6 months.[108] Several others had highly suggestive evidence including intimate partner violence[39] and unmarried women,[52] cancer survivors,[41] African/Black race,[49] placental previa,[43] hemorrhagic and hepatic disorders,[68] endometriosis,[8] chronic kidney disease,[104] and treatments for CIN.[112]

Interpretation in the light of evidence

Some of the risk factors identified from our analysis as robust are well-known risk factors and have been incorporated into the screening processes during prenatal visits such as illicit drug use, ultrasonographic markers, and reproductive history.[5] Nevertheless, we identified a few that are not receiving the attention they should during prenatal visits even though they demonstrate robust evidence.

This includes maternal psychosocial profile and sleeping quality that are either rarely screened during prenatal visits or not considered by clinicians as risk factors for PTB. Traditionally, emphasis was given to factors such as cervix length and history of PTB and their obstetric management.[5] Screening and early intervention on maternal personality disorders and SDB during pregnancy should be further evaluated at prenatal visits and potentially contribute to PTB prevention.

Interpregnancy intervals

One association with highly controversial evidence is interpregnancy interval following a miscarriage and the risk of preterm birth. The World Health Organization (WHO) encourages women who experienced a previous miscarriage to wait for a minimum of 6 months before the next conception to achieve optimal outcome and reduce obstetric complications such as preterm birth.[116] Contrary to the findings of the research on which WHO based its recommendations, some studies reported that the risk of adverse obstetric outcomes including preterm birth is lower in women who conceived less than 6 months after a pregnancy loss,[117-119] while synthesizing all available data provided the same conclusion.[108] This meta-analysis included eight studies and performed two analyses: one including the study of Conde Agudelo 2004[120] and one excluding it, and robust results were obtained after excluding this study. While this was a large retrospective study on which the WHO guidelines for delaying pregnancy for at least 6 months[116] are based, it did not differentiate between induced and spontaneous abortions and used data from many countries where induced abortion is illegal,[120] therefore should be interpreted with caution. More recent studies have criticized methods used in the previous studies; therefore, the question remains open as to the causal effect of short interpregnancy intervals after miscarriage on adverse obstetric outcomes remains unknown.[121,122] After a miscarriage, there is a very small burden on the folate reserve, and thus, miscarriage is not very likely to lead to folate deficiency in the postpartum period, so miscarriage and delivery later in pregnancy may have differential effects on subsequent pregnancy.[123,124] This could explain the reduced risk of adverse outcomes in a short IPI after a miscarriage[123] but not after delivery. In support of this hypothesis, there is evidence to suggest that late miscarriages (after 12 weeks of gestation) are associated with worse outcomes in the subsequent pregnancy.[124] In addition, most women who attempt another pregnancy soon after a miscarriage are likely to be motivated to take better care of their health and consequently result in better pregnancy outcomes.[125-127] Another plausible reason may be that those who conceive soon after a miscarriage are naturally more fertile and younger and consequently have better pregnancy outcomes. Therefore, even though the characteristics of the meta-analysis included in our assessment classified this association as robust for a protective effect, given the complex causal structure of these associations, interpretations should be made with caution.

Sleep disorders and mental health

Another risk factor with robust evidence was sleep-disordered breathing. This meta-analysis clearly demonstrated the increased risk profile of women who experience SDB not only for preterm birth but for other adverse pregnancy outcomes.[80] Regarding plausible mechanisms, the association between SDB and intermittent maternal hypoxia as well as the link with conditions synonymous with impaired placental function such as pre-eclampsia suggests a multifactorial cause, with both physiologic changes associated with pregnancy and placental dysfunction involved.[80] This robust association has clear implications for obstetric practice. First, given the rapidly increasing worldwide obesity rates, SDB is likely to become more prevalent in the pregnant population and it should be introduced in screening. Second, the increased risk for both adverse intrapartum and perinatal outcomes demonstrated in this review strongly supports the need for increased surveillance in women who experience SDB during pregnancy. Third, public health education programs must take into account the specific maternal and perinatal risks and promote education about the significance of obstructive sleep apnea symptoms and the need for women to discuss this with their obstetric caregivers. Screening for sleeping habits and suggesting more frequent follow-up for women with such symptoms have the potential to reduce the burden of PTB.

In alignment with this suggestion, women with personality disorders could be identified early through mental health screening, where targeted health interventions and multidisciplinary management can be implemented to reduce adverse outcomes for the baby/child and woman. This early identification and support also have the potential to enable the prevention of maladaptive development trajectories within the mother-infant relationship.[128,129]

The ability to modify those factors, mainly those related to mental health and sleep quality screening, through clinical interventions or public health policy measures remains to be established. Nevertheless, we need to highlight that there is no

guarantee that even a convincing observational association for a modifiable risk factor would necessarily translate into large preventive benefits for preterm birth if these risk factors were to be modified.[8]

Clinical practice and medical history

Another association that fulfilled all criteria for a robust association is the prior I-TOP with VA. Concerns have been expressed regarding the validity of the reported association mainly due to the quality of the primary studies.[130] Many of them did not adjust for strong confounders such as parity, prior PTB, race, and smoking.[98,130] The analysis of primary studies that reported data on cofounders and adjusted the risk estimated on these cofounders, revealed a greater increase in the PTB incidence.[98] This is supported by the fact that women who underwent an I-TOP usually have a low socioeconomic status and are likely to be exposed to a variety of factors related to PTB.[98] Moreover, abortion is a reported outcome that is accompanied by social stigma and, therefore, can be omitted from the medical history, leading to a high risk of differential misclassification. This highlights the need to thoroughly examine the other possible biases that can be identified in a meta-analysis even in the case that the epidemiologic criteria classify an association as robust.

Furthermore, it is important that clinical examination and medical history includes risk factors which are not well known, identified in meta-analysis with highly suggestive evidence. Regarding highly suggestive evidence, there were a few that are well known and used to classify pregnancies as high risk for PTB such as therapies for cervical intraepithelial neoplasia, advanced maternal age, placental pathology, race, first trimester bleeding, and maternal comorbidities. There were also included factors that are not routinely screened in the obstetric population such as intimate partner violence, cancer survivors, and being unmarried.

Obesity is generating an unfavorable metabolic environment from early gestation; therefore, initiation of interventions for weight loss during pregnancy might be belated to prevent or reverse adverse effects, which highlights the need for weight management strategies before conception.[75,106,107,131] Moreover, obesity is becoming a global epidemic, while assessing the strength of evidence that supports the impact of overweight and obesity in comorbidities such as sleep-disordered breathing could allow not only the identification of women at high risk for adverse outcomes including PTB, but also better prevention. PTB does not only increase the risk for maternal and infant complications, but also significantly increases a woman's risk of cardiovascular disease (CVD) after pregnancy; therefore, primary prevention of obesity could lead to multiple benefits.[132-135]

Environment

Regarding environmental risk factors, increased residential greenness was associated with a protective effect on the risk of PTB. Although this finding was categorized as having suggestive evidence, the *P*-value of the random effect estimate was very close to the stringent threshold of $< 10^{-6}$. Acknowledging the detrimental projected effect of climate change in greenness and given that it is one of the few protective risk factors for PTB,[113] serious efforts should be made to maintain and grow residential greenness. Possible mechanisms include among others amelioration of the effects of air pollutants, reduction of stress, and increase in physical activity.[113] There was also suggestive evidence for early pregnancy exposure to $PM_{2.5}$ and the risk of PTB. This association has been debated in the literature with conflicting results about the timing and magnitude of effect and is less robust than other associations that have been shown to have strong evidence for associations[136] such as birth weight.

Strengths and limitations

To our knowledge, this umbrella review represents the most comprehensive overview of published literature of observational studies to date investigating associations between a wide array of risk factors and PTB. The epidemiological robustness of meta-analyses of observational studies was assessed against a transparent and replicable set of statistical criteria. In addition, we performed a deeper assessment of these associations and assessed their potential to test causal assumptions. Our assessment has certain limitations. Umbrella reviews focus on existing systematic reviews and meta-analyses and therefore some studies may have not been included either because the original systematic reviews did not identify them, they were too recent to be included, or they did not provide the data to be included. In the current assessment, we used all available data from observational studies; therefore, the meta-analysis estimates may partly reflect the biases in the primary studies. Statistical tests of bias in the body of evidence (small-study effect and excess significance tests) offer hints of bias, not definitive proof thereof, while the Egger test is difficult to interpret when the between-study heterogeneity is large. These tests have low power if the meta-analyses include less than 10 studies and they may not identify the exact source of bias.[22,24,34] More specifically, in our study, all robust evidence applied to meta-analyses with less than 10 studies; therefore, the results of publication bias should be interpreted with caution. Furthermore, we did not appraise the quality of the individual studies on our own, since this should be included in the original meta-analysis and it was beyond the scope of the current umbrella review. However, we recorded whether and how they performed a quality assessment of the synthesized studies. Lastly, we cannot exclude the possibility of selective reporting for some associations in several studies. For example, perhaps some risk factors were more likely to be reported, if they had statistically significant results. Diving deeper into the associations that were classified as robust, we detected some issues beyond the prespecified criteria that are traditionally applied for umbrella reviews.

Therefore, it is recommended that future umbrella reviews perform a comprehensive assessment of the associations beyond the classic criteria.

Conclusions

The present umbrella review of meta-analyses identified 166 unique risk factors for preterm birth. Our analysis identified seven risk factors with robust evidence and strong epidemiological credibility pertaining to isolated single umbilical artery, amphetamine exposure, maternal personality disorder, sleep-disordered breathing, induced termination of pregnancy with vacuum aspiration, low gestational weight gain, and interpregnancy interval following miscarriage of less than 6 months, but the results should be interpreted with caution. As previously suggested, the use of standardized definitions and protocols for exposures, outcomes, and statistical analyses may diminish the threat of biases, enhance comparability of different studies examining risk factors, and promote the development

and training of prediction models that could identify high-risk populations and promote public health.

Abbreviations

25-OHD	25-Hydroxyvitamin D
APS	Antiphospholipid syndrome
BMI	Body mass index
CIN	Cervical intraepithelial neoplasia
CIs	Confidence intervals
CKD	Chronic kidney disease
CL	Cervical length
CVD	Cardiovascular disease
GWG	Gestational weight gain
HPV	Human papillomavirus
IPI	Interpregnancy interval
I-TOP	Induced termination of pregnancy
IVF	In vitro fertilization
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of transformation zone
LT4	Levothyroxine
MESH	Medical Subject Headings
MINORS	Methodological index for non-randomized studies
NO_2	Nitrogen dioxide
NRT	Nicotine replacement therapy
NVDI	Normalized difference vegetation index
OC	Oral contraceptive
PCOS	Polycystic ovary syndrome
PI	Prediction interval
PM_{10}	Particulate matter with aerodynamic diameter less than or equal to 10 µm
$PM_{2.5}$	Particulate matter with aerodynamic diameter less than or equal to 2.5 µm
PTB	Preterm birth
PTL	Preterm labor
RR	Relative risk
SDB	Sleep-disordered breathing
SMM	Severe maternal morbidity
S-TOP	Spontaneous termination of pregnancy
T1DM	Type 1 diabetes mellitus
TB	Tuberculosis
TOP	Termination of pregnancy
TVU	Transvaginal ultrasound
WHO	World Health Organization

Supplementary Information

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Authors' contributions

GM, SP, EE, and AE conceptualized the idea for the manuscript. IM, EE, AE, TK, EB, GM, and SP contributed to the methods for the paper. SP and IM drafted the manuscript under the supervision of EE and GM. All authors read and approved the final manuscript. SP is the guarantor of this manuscript and is responsible for the overall content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Availability of data and materials

Relevant data to our study are mainly included in the article, tables, and supplemental material. However, we will share the original dataset after reasonable requests.

Declarations

Ethics approval and consent to participate

No patients or members of the public were directly involved in this study as no primary data were collected.

Competing interests

The authors declare that they have no competing interests.

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and metabolites and their functional role in contributing to the benefits of infant nutrition," the study authors wrote.

Low Birth Weight and Overweight at 20 Raise T2D Risk 10-Fold

Men with low birth weight who go on to be overweight in young adulthood have a nearly 10-fold increased risk of developing type 2 diabetes, reveals Swedish research that indicates the risks can nevertheless be reduced if overweight in young adulthood is avoided. The researchers gathered data on birth weight and height and weight measurements for men from the population-based body mass index (BMI) Epidemiology Study Gothenburg cohort born between 1945 and 1961. School healthcare records were accessed, alongside records for military conscription, which was mandatory for all Swedish men until 2010. The main exposures were birth weight, childhood overweight at 8 years of age, and young adult overweight at 20 years of age, from which age-adjusted BMI estimates were calculated. The individuals were then linked to the Swedish National Patient Register to identify diagnoses of type 2 diabetes after 30 years of age to avoid misclassification with type 1 diabetes. The team included 34,321 men, who were followed up from 30 years of age to December 31, 2019, yielding 1,100,000 person-years of follow-up. Over a median follow-up of 34.3 years, 2733 cases of type 2 diabetes were diagnosed, at a median age of 59.4 years. Birth weight below the median of 3.6 kg and overweight at age 20, but not overweight at age 8, were associated with an increased risk for both early (≤ 59.4 years) and late type 2 diabetes (> 59.4 years). A birth weight below the median plus overweight at age 20 years was associated with a marked increased risk for early diabetes, at a hazard ratio of 6.07, rising to 9.94 among men with low birth weight (≤ 2.5 kg) and overweight at 20 years. The team noted: "Importantly, we observed a 21% absolute risk reduction for early type 2 diabetes if an individual with a low birth weight avoided overweight in young adulthood." "We therefore propose that particular efforts should be directed at children with low birth weight to prevent the subsequent development of young adult overweight and the associated massive risk of type 2 diabetes." Coauthor Jenny M. Kindblom, MD, PhD, from Sahlgrenska University Hospital, Gothenburg, Sweden, suggested in a release: "It's possible that the metabolic consequences of fetal growth restriction…when combined with a detrimental BMI trajectory during puberty, when the insulin resistance is at a lifetime peak due to the surge of growth and sex hormones, result in an additive excess risk for later type 2 diabetes." The research was led by Jimmy Célind, MD, Department of Paediatrics, Institute of Clinical Studies, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Pessary or Progesterone for Preterm Birth? Advantage Med

A study comparing cervical pessary and vaginal progesterone for the prevention of preterm birth in women with a short cervix of ≤ 35 mm found no significant difference between the interventions for perinatal complications. Among women with a cervical length of ≤ 25 mm, however, pessaries appeared to be less effective at preventing spontaneous preterm birth and adverse outcomes, according to the researchers. Researchers conducted an open-label, randomized controlled trial at 20 hospitals and five obstetric ultrasound practices in the Netherlands. The study included 635 women with healthy singleton pregnancies between 18 and 22 weeks' gestation and an asymptomatic short cervix of ≤ 35 mm. Participants had no history of spontaneous preterm birth. Women were randomly assigned to receive either an Arabin cervical pessary or 200 mg/d vaginal progesterone for ≤ 36 weeks of gestation. The investigators examined a composite measure of adverse perinatal outcomes, including periventricular leukomalacia (grade, > 1), chronic lung disease, intraventricular hemorrhage (grade, III or IV), necrotizing enterocolitis (stage, > 1), sepsis, stillbirth, and death of the baby. Adverse perinatal outcomes occurred in 6% of each treatment group, and the rate of spontaneous preterm birth did not differ significantly between the groups. In a subgroup analysis of 131 patients with a cervical length of ≤ 25 mm, spontaneous preterm birth at < 28 weeks occurred more often in the pessary group (16% vs 4%). Adverse perinatal outcomes also seemed to occur more frequently in the pessary group (24% vs 12%; relative risk, 2.1 [95% CI, 0.95-4.60]), in the subgroup analysis, according to the researchers. "Even though the study was not powered for the subgroup with a short cervix of ≤ 25 mm, results suggest that a cervical pessary should not be used as preventive treatment in this group," the researchers wrote. The study was led by Charlotte E van Dijk, MD, with Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands. It was published online on March 12, 2024, in *The BMJ*.

Pain Exposure Hinders Brain Development in Preterm Infants

Early life pain exposure alters brain development in preterm infants, particularly female infants, according to a new study. The observational cohort study collected and analyzed data from 150 infants born at less than 32 weeks' gestation. Its findings demonstrated that early life exposure to pain affects brain development in very preterm infants. Additionally, the investigators found sex-specific associations between pain exposure and brain development, with female infants experiencing a greater impact on brain connectivity. "Painful exposures are part of lifesaving care for these babies in the neonatal intensive care unit [NICU]. Our work emphasizes that you need to discover new ways to treat pain in preterm babies that promote brain development," study author Thiviya Selvanathan, MD, PhD, a pediatric neurologist at BC Children's Hospital and assistant professor of pediatrics at the University of British Columbia in Vancouver said. The study was published March 15 in *JAMA Network Open*. With novel imaging tecÚology, researchers can look at the brain in a new way, said Selvanathan. Specifically, "we have the tools to now look at the brain connectome," which maps how connections in the brain are formed, she said. "Instead of looking at individual brain regions, we can now look at how they interact and work together." The study collected MRI data from 80 male and 70 female infants treated at two NICUs in Toronto between 2015 and 2019. All infants were delivered before term, with a median gestational age at birth of 27.1 weeks. Pain was quantified as the total number of invasive procedures in the initial weeks after birth. In the full cohort, the investigators found that greater early life pain was associated with decreased regional connectivity in the neonatal brain, which in turn was associated with worsened neurodevelopmental outcomes at 18 months. The brain's ability to perform both specialized processing and integrating information from various brain regions was hindered. When the researchers stratified the results by sex, they found that

greater pain exposure was associated with slower maturation of structural connectivity among female infants only. The finding suggests that these infants may be more vulnerable to the effects of early life pain. However, Selvanathan noted that more research is needed to understand why this sex-specific difference may exist.

Safety Risks Persist With Out-of-Hospital Births

Safety concerns persist for out-of-hospital births in the United States with multiple potential risk factors and few safety requirements, according to a paper published in the *American Journal of Obstetrics and Gynecology*. In 2022, the Centers for Disease Control and Prevention (CDC) reported the highest number of planned home births in 30 years. The numbers rose 12% from 2020 to 2021, the latest period for which complete data are available. Home births rose from 45,646 (1.26% of births) in 2020 to 51,642 (1.41% of births). Amos Grünebaum, MD, and Frank A. Chervenak, MD, with Northwell Health, and the Department of Obstetrics and Gynecology, Lenox Hill Hospital, Zucker School of Medicine in New Hyde Park, New York, reviewed the latest safety data surrounding community births in the United States along with well-known perinatal risks and safety requirements for safe out-of-hospital births. "Most planned home births continue to have one or more risk factors that are associated with an increase in adverse pregnancy outcomes," they wrote.

COVID Vaccination Protects Against Infection-Related Risks for Stillbirth and Preterm Birth

Previous research has established that there is an increased risk for stillbirth and preterm birth after SARS-CoV-2 infection in pregnancy. A new study finds that the timing of infection during pregnancy matters, with early infection being a worse risk factor than late infection for the two outcomes. The study also finds that COVID vaccination may protect against the infection-related risks for stillbirth and preterm birth. The absolute rate of stillbirth across this cohort of infected pregnant women was very low (0.87%), whereas the rates of early preterm birth (2.05%) and late preterm birth (8.34%) were higher. Vaccination against COVID reduced the risk for stillbirth by a significant 68% compared with no vaccination. Vaccination also reduced the risks for early preterm birth by a non-significant 35% and late preterm birth by a significant 27% compared with no vaccination.

Delaying Inguinal Hernia Repair Beneficial for Preterm Infants

A clinical trial of preterm infants with inguinal hernia found that performing repair after discharge from the neonatal intensive care unit (NICU) resulted in less adverse events than procedures prior to discharge. The study compared the safety of repair before discharge from the NICU with repair after discharge and post-55 weeks gestational plus chronological age (postmenstrual age). The study randomized 338 infants from 39 US hospitals to early or late repair; of the 320 infants who had the surgery, 86% were male, 30% were Black, and 59% were White. The primary outcome was the occurrence of at least one serious adverse event over the 10-month observation period, including apnea requiring respiratory intervention, intubation for more than 2 days, bradycardia requiring pharmacological intervention, or death. Secondary outcomes included a total number of days in the hospital, including the initial NICU stay after randomization, postoperative hospitalization, and any inpatient days due to hospital readmission over the course of the following 10-month period. Infants who underwent late repair had a lower probability of having at least one serious adverse event: 28% had at least one adverse event in the early group vs 18% in the late group. Infants in the late repair group had shorter stays in the NICU after randomization, as well as fewer hospital days following surgery. Late repair provided the greatest benefit to infants with a gestational age younger than 28 weeks and those who had bronchopulmonary dysplasia. Hernias resolved spontaneously in 4% of infants in the early repair group and 11% in the late group, which the authors said supports delaying hernia repair. "The decision to treat the inguinal hernia with an early or late repair strategy likely does not influence the overall duration of the neonatal intensive care unit stay but may hasten the discharge by several days if later repair is chosen, which is likely important to parents and neonatologists." The study was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Martin L. Blakely, MD, MS, from the Department of Surgery at the University of Texas Health Science Center, Houston, Texas, is the corresponding author.

Many Hospitals in China Stop Newborn Delivery Services as Birth Rate Drops

Many hospitals in China have stopped offering newborn delivery services this year, state-backed news outlet Daily Economic News reported, with industry experts warning of an "obstetric winter" due to declining demand amid a record drop in new births. Hospitals in various provinces including in eastern Zhejiang and southern Jiangxi have in the past two months announced that they will close their obstetric departments. The Fifth People's Hospital of Ganzhou City in Jiangxi said on its official WeChat account that obstetric services would be suspended. Zhejiang's Jiangshan Hospital of Traditional Medicine announced on its WeChat page that its obstetrics business would stop from Feb. 1. The closures come as Chinese policymakers grapple with how to boost young couples' desire to have children as authorities face a growing demographic headache of a rapidly ageing society. China's population fell for a second consecutive year in 2023 as the record-low birth rate and high deaths due to COVID-19 accelerated a downturn that officials fear will have profound long-term effects on the economy's growth potential. The most recent available data from China's National Health Commission showed the number of maternity hospitals dropped to 793 in 2021 from 807 in 2020.

Neonatal Abstinence Syndrome Declined in BC During Pandemic

Neonatal abstinence syndrome (NAS) increased in British Columbia (BC), Canada, prior to the pandemic, then decreased across both urban and rural locations in the first 2 years of the pandemic, new research suggested. The cross-sectional study of more than 514,000 live births showed a relative increase in the NAS rate of 0.5% per month from 2010 to 2020, and a 1.3% per month decrease during the pandemic (June 2020-March 2022). The results were "unexpected because studies have documented increased opioid use during the pandemic," the authors noted. However, the increase was not matched by a continued increase in NAS. The study was initiated because of the "large increase" in opioid overdose deaths during the pandemic, lead author Sarka Lisonkova, MD, PhD, of the Women's Hospital and Health Centre of British Columbia, Vancouver, Canada, said.

"This rise was so substantial that it led to discussions about a 'dual epidemic', with deaths from illicit drug overdoses outnumbering those from COVID-19. In light of this situation, we sought to investigate whether there was a corresponding increase in the rates of NAS." The study included registry data for 514,189 live-born infants, of which 2165 had NAS (4.2 per 1000 live births). Between fiscal years 2010-2011 and 2019-2020 (prepandemic period), NAS increased from 2.6 to 4.8 per 1000 live births. NAS rates were highest in fiscal year 2020-2021 and decreased in 2021-2022 from 5.6 to 4.7 per 1000 live births, respectively. The direction of the temporal trend in NAS rates changed after the onset of the pandemic in June 2020. The relative increase in the NAS rate during the prepandemic period (March 2010-May 2020) was 0.5% per month, whereas the NAS rate decreased by 1.3% per month during the pandemic period (June 2020-March 2022).

Finding the Best Respiratory Support Strategies for Premature Babies

Chris Campbell

Anyone who has ever seen a premature baby has likely had their heart broken.

That's because these tiny, fragile humans face such a long, uphill battle that requires volumes of strategic planning by a team of medical professionals every step of the way.

One of the biggest issues faced by neonates who are born preterm is poor lung development, plus the risk of lung injury caused by the thing that's trying to help them breathe — respiratory support.

As the neonate struggles to grow, their breathing mechanics will continue to change and any ventilator strategy must be adjusted along with those changes and be designed to be as non-invasive as possible. This ranges from the early days after birth all the way to even school age, meaning strategies are needed amid the transition to home. This transition includes reducing the strain on caregivers feeling the burden of home care amid the risks of preventable mortality.

A 2023 review argues that more study is "desperately needed" into finding better ventilator strategies for children with severe bronchopulmonary dysplasia (BPD), especially in the area of "timing of transition to chronic respiratory support and the optimal chronic ventilatory strategies.

This is according to the review by Erik B. Hysinger and Shawn K. Ahlfeld out of the University of Cincinnati College of Medicine, Cincinnati Children's Hospital, who advocated for more prospective trials into the issue.

The authors detailed in their review the long road faced by many neonates who are born preterm, and how "gentle" strategies are needed for respiratory support.

"Early in the disease course respiratory support should focus on limiting additional lung injury by utilizing non-invasive ventilation or 'gentle' invasive mechanical ventilation with a low tidal volume, short inspiratory time, and high respiratory rate strategy," the authors write. "However, for those infants who go on to need chronic respiratory support, worsening obstructive lung disease requires a transition to longer inspiratory times, lower rates, and a higher tidal volume strategy to optimize ventilation."

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

The authors said other reviews have looked into surrounding issues[1-21] and provided "excellent" information on the "safety and efficacy of non-invasive modes of respiratory support."

The review also delves into issues when the neonate gets older and how these issues have been studied.

"While the majority of infants require a period of invasive mechanical ventilation, by 36 weeks' corrected gestational age, more than 90% will have been extubated and supported non-invasively,"[16,21] the authors write. "…comparing the efficacy of various modes of non-invasive support is emerging, but presently nCPAP comprises the bulk of available data. Since 2008, 5 large multicenter RCTs (COIN,[9] SUPPORT,[17] CURPAP,[19] Vermont Oxford,[18] and now OPTIMIST-A[20]) have enrolled over 3,000 infants born at 24-29 weeks' gestation and cared for with nCPAP and, therefore, provide a wealth of safety and efficacy data. However, despite wide-spread acceptance and use of non-invasive ventilation in both the United States (10) and United Kindom,[22] nearly 50% of surviving infants continue to develop BPD.[16,21] Preclinical and clinical evidence implies that outcomes may be improved by prolonging the duration of constant distending pressure. A strategy employing prolonged, prophylactic support on nCPAP until respiratory stability is achieved and infants can be weaned directly to room air is associated with the lowest rates of BPD.[23]

"Supporting evidence derived from preclinical animal models demonstrates that constant distending pressure minimizes lung injury and augments lung growth. In both murine and rabbit models of hyperoxic neonatal lung injury, compared to no support, use of CPAP reduced inflammation, preserved alveolar-capillary development, and durably improved lung function.[24,25] Exposure of juvenile ferrets to 2 weeks of constant distending pressure significantly increased lung weight and DNA content and increased total lung capacity by 40% while preserving elastic recoil, thus implying CPAP induced not merely lung distension but lung growth.[26] In infants with severe congenital diaphragmatic hernia, tracheal occlusion (resulting in lung fluid retention and constant distension of the developing lungs) improved survival and reduced the need for ECMO, strongly-implying improved lung function.[27] Recent clinical evidence indicates that extremely preterm infants with evolving BPD may similarly benefit from prolonged constant distending pressure."

The Long Term

The review also detailed the sad situation faced by some premature infants who aren't able to wean from positive pressure ventilation, meaning they will need chronic ventilation support.

But there is also a lack of information on different strategies, the authors write.

"There is no clear timing when providers should transition to chronic ventilator strategies, and there is wide variation based on center,"[28] say the authors. "However, once it has been determined that an infant with BPD will be treated with chronic mechanical ventilation, the ventilation strategy should shift. While there should be continued efforts to minimize lung injury as much as possible, the primary focus transitions to providing optimal respiratory support for patient comfort, growth and development, and gas exchange, which appears to improve in neonates with BPD following placement of a tracheostomy tube and chronic mechanical ventilation.[29] Currently, there is an extreme paucity of data comparing different chronic ventilator strategies in established severe BPD; consequently, a physiologic approach to mechanical ventilation must be considered."

The review details the use by care providers of a series of time and flow triggers for chronic mechanical ventilation, but add that some patients may have delayed or failed triggers.

"In one report, a majority patients with severe BPD treated with chronic mechanical ventilation experienced failed triggers, with nearly 15% of breaths resulting in a wasted effort," said the authors. "The inability to trigger, results in patient ventilator dysnchronization and patient discomfort. This may manifest with agitation, hypoxemic episodes, poor ventilation, and increased need for sedation."[30]

The report also looks as gas exchange, PEEP, tidal volumes and mandated respiratory rates.

The review also circles back to the difficulties with the transition to home due to the lack of data on the subject.

"In general, most providers will attempt to transition to the home ventilator on settings consistent with the hospital ventilator. In some situations, it may not be possible to achieve identical settings. Trigger sensitivity is less for home ventilators, which can lead delayed or failed triggers during the transition. Further, hospital ventilators may allow a longer inspiratory time than is feasible on a home ventilator, particularly with smaller tidal volumes, which can be problematic in children who need long inspiratory times to ensure recruitment of regions with long time constants."[31]

Caregivers at home face anxiety and even depression if they don't have access to home nursing support.[32-34]

"Fatigue is of particular importance as in-home mortality in this population exceeds 15%, and many of the events resulting in the patient's demise are preventable or treatable e.g., mucus plugs or accidental decannulation rather than progression of the underlying lung disease,"[35-38] the authors write. "Because of the risks, most programs provide extensive training for caregivers of technology-dependent children that center on management of the tracheostomy, ventilator, and all other equipment that will be necessary to meet the child's needs at home. Caregivers should also be trained in cardiopulmonary resuscitation and patient transfers."

The review also said study is needed on weaning chronic mechanical ventilation, as well as weaning non-invasive support.

"As with weaning of mechanical ventilation, there is precious little data for the optimal strategies to wean non-invasive support following hospital discharge," the authors write.

Conclusion

In the end, the authors strongly urge more study.

"Ventilator strategies for children born premature evolve as the disease process progresses," they say. "While there is currently a wealth of information highlighting the use of lung protective strategies with non-invasive positive pressure ventilation or invasive ventilation with small tidal volumes and high mandatory rates during the earliest phase of disease, there is a dearth of data about the timing of transition to chronic respiratory support and the optimal chronic ventilatory strategies. Ultimately, children will gradually wean from support, typically by school-age. Prospective trials that establish optimal ventilator strategies for children with severe established BPD are desperately needed, and the need for such studies continues to grow as the limit of viability is decreased and more children will need chronic mechanical ventilation."

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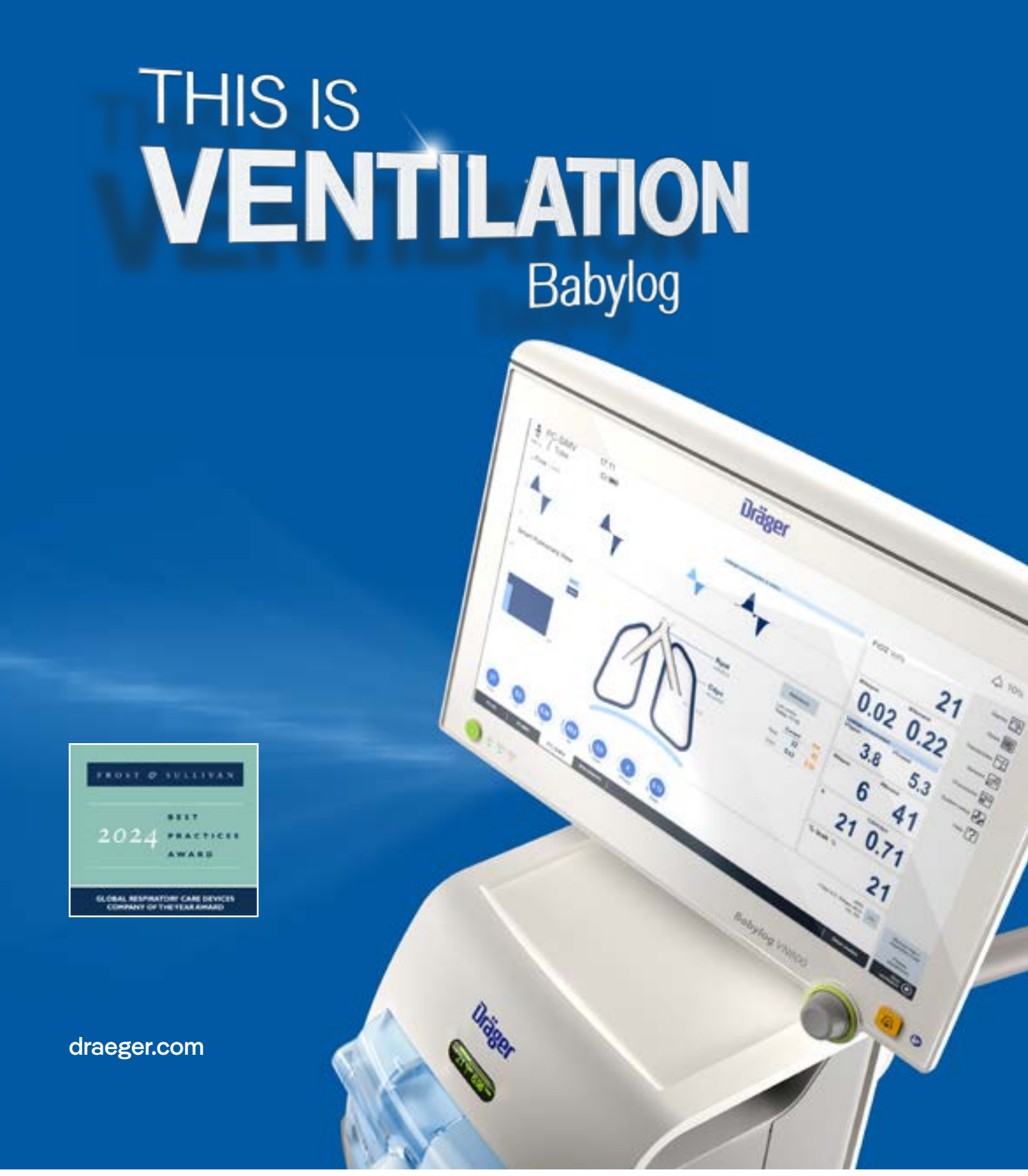

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