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Postnatal steroids to prevent bronchopulmonary dysplasia in high-risk preterm infants

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POSTNATAL STEROIDS TO PREVENT BRONCHOPULMONARY DYSPLASIA IN HIGH-RISK PRETERM INFANTS

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is diagnosed in approximately 40% of extremely preterm infants, those born before 28 weeks' gestational age, and affects roughly 10,000 to 15,000 infants annually in the United States alone. Current treatment of BPD aims to not only aid in the survival of the infant but to also minimize further lung damage and promote physiologic growth to enhance lung development and repair. As the pathogenesis of the disease is multifactorial, including pre-, peri-, and postnatal factors, treatment and prevention approaches to BPD are diverse and include both medical treatment and ventilation strategies. Late postnatal steroids (> 7 days of life) have been proven to facilitate extubation and reduce the incidence of BPD in preterm infants. However, there is evidence that the use of steroids may contribute to increased rates of neurological impairment, including increased incidence of cerebral palsy. Given these findings, the American Academy of Pediatrics (AAP) guidelines recommend against the routine use of systemic steroids in the prevention of BPD and instead argues its use should be limited to infants who are considered extremely high-risk. The aim of this study is to determine whether the use of postnatal dexamethasone decreases the risk of developing BPD in a subset of high-risk infants, those with a concomitant diagnosis of necrotizing enterocolitis or late onset sepsis. A sample size of 200 extremely preterm infants with either necrotizing enterocolitis (NEC) and/or sepsis will be enrolled in a

multi-center double-blinded randomized controlled trial comparing a low-dose dexamethasone taper and saline placebo. Infants will be evaluated for the development of BPD based on respiratory support and supplemental oxygen requirement at 36 weeks' post-menstrual age (PMA). Infants will also be evaluated for presence of neurodevelopmental outcomes at 18- to 22-months follow-up. The results of this proposed study will build the evidence base for the safety and efficacy of postnatal steroids in the prevention of BPD in a subset of high risk, extremely preterm infants. This will help to establish a more detailed characterization of infants for which the benefits of steroids outweigh the risks. The results will enable clinicians to make more informed decisions regarding the medical care of extremely preterm infants and more accurately counsel parents on the incidence of subsequent BPD development, as well as long-term morbidities.

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LIST OF ABBREVIATIONS

AAP..... American Academy of Pediatrics

ART..... Assisted Reproductive Technology

BMC..... Boston Medical Center

BPD.....Bronchopulmonary Dysplasia

BWH .....Brigham and Women's Hospital

CPAP.....Continuous Airway Pressure

CRP .....C-Reactive Protein

ELBW .....Extremely Low Birth Weight

EMR.....Electronic Medical Records

FiO2 ..... Fraction of Inspired Oxygen

HINE.....Hammersmith Infant Neurological Examination

IL-1β ..... Interleukin-1 Beta

IL-6 .....Interleukin-6

IL-8 .....Interleukin-8

INF-γ ..... Interferon-gamma

LBW..... Low Birth Weight

NEC..... Necrotizing Enterocolitis

NHLBI .....National Heart, Lung and Blood Institute

NICHD.....National Institute of Child Health and Human Development

NICU.....Neonatal Intensive Care Unit

NRN ..... Neonatal Research Network

ORD ..... Office of Rare Diseases

PECAM-1 ..... Platelet and Endothelial Cell Adhesion Molecule 1

PH ..... Pulmonary Hypertension

PMA ..... Post-Menstrual Age

RCT ..... Randomized Controlled Trial

RDS ..... Respiratory Distress Syndrome

sFlt-1 ..... Fms-like Tyrosine Kinase 1

SGA ..... Small for Gestational Age

SIRS ..... Systemic Inflammatory Response Syndrome

TNF-α ..... Tumor Necrosis Factor Alpha

VEGF ..... Vascular Endothelial Growth Factor

VLBW ..... Very Low Birth Weight

WHO ..... World Health Organization

INTRODUCTION

Background

According to the Centers for Disease Control, preterm birth, a birth taking place before 37 weeks of gestational age, affects nearly one in ten children born in the United States.[1] Historically, infants born prematurely had a very limited chance of survival. However, in the recent decades with advances in perinatal and neonatal care, outcomes have vastly improved. The widespread establishment of neonatal intensive care units (NICUs), as well as the use of exogenous surfactant therapy, antenatal steroids, and improved mechanical ventilators, has decreased the mortality rates among preterm infants who previously had little chance of survival.[2]

With increased survival rates, however, there is concern of short- and long-term morbidity among preterm infants. One of the most common complications of preterm birth is bronchopulmonary dysplasia (BPD), a chronic lung disease affecting infants that require mechanical ventilation and supplemental oxygen therapy for respiratory distress syndrome (RDS).[3] BPD affects around 40% of extremely preterm infants, those born before 28 weeks' gestational age, and comprises roughly 10,000 to 15,000 infants annually in the United States alone.[3,4] The disease was first characterized in 1967 but, as technology and medical therapy have improved and as increasingly immature preterm infants have survived, the pathologic findings and clinical course of BPD have evolved.[5,6] The "new" description of BPD is defined by the arrest of lung development and inflammation with accompanying pro-inflammatory cytokine response and fibrosis.[7]

BPD is a complex medical condition without a known cure.[8] Current treatment of BPD aims to not only aid in the survival of the infant but to also minimize further lung damage and promote physiologic growth to enhance lung development and repair. As the pathogenesis of the disease is multifactorial, including pre-, peri-, and postnatal factors, the treatment and prevention approaches to BPD are diverse and include both medical treatment and ventilation strategies.[3,4]

Statement of the Problem

Late postnatal steroids (> 7 days of life) have been proven to facilitate extubation and reduce the incidence of BPD in preterm infants.[3] However, there is evidence that the use of steroids may contribute to increased rates of neurological impairment, including increased incidence of cerebral palsy.[9] Given these findings, the American Academy of Pediatricians (AAP) guidelines recommend against the routine use of systemic steroids in the prevention of BPD.[10,11] Rather, the AAP argues its use should be limited to "exceptional clinical circumstances," such as infants who are unable to be extubated or are considered extremely high-risk.[11]

Clinical practices currently vary substantially between hospitals, as it remains unclear which infants merit the designation of high-risk and would benefit from postnatal steroids.[3] At Boston Medical Center and Brigham and Women's Hospital, infants with necrotizing enterocolitis (NEC) and/or sepsis who require prolonged mechanical ventilation are often administered corticosteroids, although the assessment differs from

physician to physician. The field lacks evidence that these subsets of preterm infants benefit from a course of postnatal steroids.

Hypothesis

The use of late postnatal low-dose dexamethasone in extremely preterm infants with necrotizing enterocolitis and/or sepsis will decrease the risk of BPD at 36 weeks' postmenstrual age without negatively impacting neurodevelopmental outcome.

Objectives and specific aims

While the AAP recommends to conserve the use of postnatal corticosteroids to preterm infants at high risk of developing BPD, clinical practices vary widely as there are no clear defining factors to determine which subsets should be considered high risk. The objective of this study is to further explore the risks and benefits of the use of postnatal dexamethasone in the prevention of BPD in infants with necrotizing enterocolitis and/or sepsis. Specific aims of the study are as follows:

1. To determine whether the use of postnatal dexamethasone decreases the risk of developing BPD in infants with a concomitant diagnosis of necrotizing enterocolitis and/or sepsis.
2. To compare the effects of low-dose dexamethasone treatment on length of time on ventilation and supplemental oxygen among infants with necrotizing enterocolitis and/or sepsis

3. To determine if low-dose dexamethasone in the setting of necrotizing enterocolitis and/or sepsis is associated with neurodevelopmental impairment at 18 to 22 months of age

REVIEW OF THE LITERATURE

Overview of Preterm Birth

Preterm birth, or birth earlier than 37 weeks of gestation, affects an estimated 15 million babies each year.[1,12] The United States is the only resource-rich country that continuously ranks as having one of the highest rate of preterm births globally.[1] Infants born preterm are often sub-categorized based on gestational age (GA). The World Health Organization (WHO) defines infants as moderate to late preterm, very preterm, and extremely preterm based on gestational age (Table 1).[13] However, as low birth weight is a frequent concurrent finding amongst this population, preterm infants may also be categorized based on birth weight independent of gestational age (Table 2).[14]

Table 1: Classification of Preterm Infants Based on Gestational Age

	Gestational Age
Moderate to Late Preterm	32-37 weeks GA
Very Preterm	28-32 weeks GA
Extremely Preterm	<28 weeks GA

Table 2: Classification of Preterm Infants Based on Birth Weight

	Birth Weight
Low Birth Weight (LBW)	<2500 g (<5 lb. 8 oz)
Very Low Birth Weight (VLBW)	<1500 g (<3 lb. 5 oz)
Extremely Low Birth Weight (ELBW)	<1000 g (<2 lb. 3 oz)

Rates of preterm birth in the United States have been rising over recent years for a number of reasons, including increased rates of obesity and hypertension, lack of access to sufficient prenatal care, and tobacco use.[15] Thirty percent of preterm births are caused by multiple gestation, often in the setting of artificial reproductive technology (ART).[1,12,16] Other known causes of preterm birth include genital tract infections, cervical incompetence, and premature rupture of membranes.[12] While many of these risk factors can be identified early and prevented with methods such as cervical cerclage, bed rest, and prophylactic tocolytic therapy, 30% of preterm births are idiopathic.[12,17]

Preterm birth is the leading cause of neonatal mortality in the United States and can cause significant morbidity in infancy and into childhood.[12] Developmental immaturity associated with preterm birth affects nearly every organ system in an infant, leaving one more susceptible to acute neonatal illnesses and complications throughout childhood.[18] The most common complications of prematurity include pulmonary and neurologic injury, however necrotizing enterocolitis (NEC) and sepsis are also very common.[18,19] Below, the respiratory system and its complications associated with preterm birth will be discussed. However, complications associated with a premature nervous system will not be discussed as it is beyond the scope of this study.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is an acute respiratory illness associated with surfactant deficiency that primarily affects neonates born before 37 weeks of gestation.[20] The incidence of RDS increases with decreased gestational age, as well as decreased birth weight, male sex, and birth by cesariansection.[21] Of note, among infants born before 27

weeks of gestation, 80% will develop RDS.[18] The severity of RDS can range from the need for low supplemental oxygen to severe respiratory failure requiring mechanical ventilation.[22] While RDS is less common in infants born after 33 weeks of gestation, it remains a serious medical condition that can result in sustained lung dysfunction.[18,20]

Introduction to Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that is the most serious and significant sequelae of RDS, affecting roughly 10,000 to 15,000 infants annually in the United States alone.[4] Among infants born between 22 and 28 weeks' gestation, its incidence rate is as high at 68%.[5,23] BPD is relatively uncommon in those whose birth weight is greater than 1250 grams or whose gestational age is greater than 30 weeks.[24] The disease was first characterized in 1967 when Northway et al reported clinical, radiological, and pathological changes seen in premature infants with severe RDS who had been treated with prolonged mechanical ventilation and high oxygen supplementation (concentrations of oxygen = 80-100%).[6] This is now referred to as the "old BPD."

While the definition of BPD historically has lacked uniformity and, even today, can be quite variable among medical practices, the most common clinical definition is based on prolonged supplemental oxygen requirement.[18,25,26] In 2000, the National Heart, Lung and Blood Institute (NHLBI) partnered with both the Office of Rare Diseases (ORD) and the National Institute of Child Health and Human Development (NICHD) to review the definition of BPD.[27] The new definition that was developed as a result of this partnership takes into consideration positive pressure requirements, total duration of

oxygen supplementation, and gestational age (Table 3).[3,27] Furthermore, these diagnostic criteria have been validated as effective in identifying a risk-based spectrum of the disease more accurately than previously definitions.[28]

Table 3: Diagnostic Criteria for Bronchopulmonary Dysplasia (Adapted from Jobe & Bancalari)[27]

Gestational Age	***< 32 weeks***	***≥ 32 weeks***
Time of Assessment	*36w postmenstrual age or time of discharge*	*Between 29-55d postnatal age or time of discharge*
	Treatment with oxygen >21% for at least 28 days ***plus:***	
Mild BPD	Breathing room air	
Moderate BPD	Need for < 30% oxygen	
Severe BPD	Need for ≥ 30% oxygen and/or positive pressure	

Short- and Long-Term Outcomes of BPD

Approximately 25% of infants with BPD are identified as having pulmonary hypertension (PH), characterized by elevated pulmonary pressures.[3] BPD-associated PH has been found to result in mortality rates between 14% and 38%.[3] Although this rate has decreased due to recent advances in the management of PH, those who survive are significantly more likely to have neurodevelopmental impairments.[29] The diagnosis of BPD is also associated with respiratory morbidities into childhood and even adulthood.[30,31] These respiratory morbidities include increased risk of respiratory illness, decreased lung function, increased incidence of emphysema, and a higher frequency of wheezing episodes.[32] Recent data has also found that adolescents and adults with BPD as

an infant may show signs of decreased right ventricular function, increased cardiovascular risk, and higher incidence of arterial hypertension.[32]

Pathogenesis and Pathophysiology of BPD

Overview of Fetal Lung Development

To effectively understand the pathophysiology of BPD, it is necessary to review the stages of normal lung development in the human body. There are five stages of lung development, including embryonic, pseudoglandular, canalicular, saccular, and alveolar (Figure 1).[7] The embryonic stage begins between 4 and 7 weeks' gestation and involves the formation of two buds emerging from the ventral foregut with successive branching to form lobar and segmental airways.[7] Cellular differentiation continues into the pseudoglandular stage, where adult structures of cartilage, vasculature, bronchial smooth muscle, and submucosal glands begin to form.

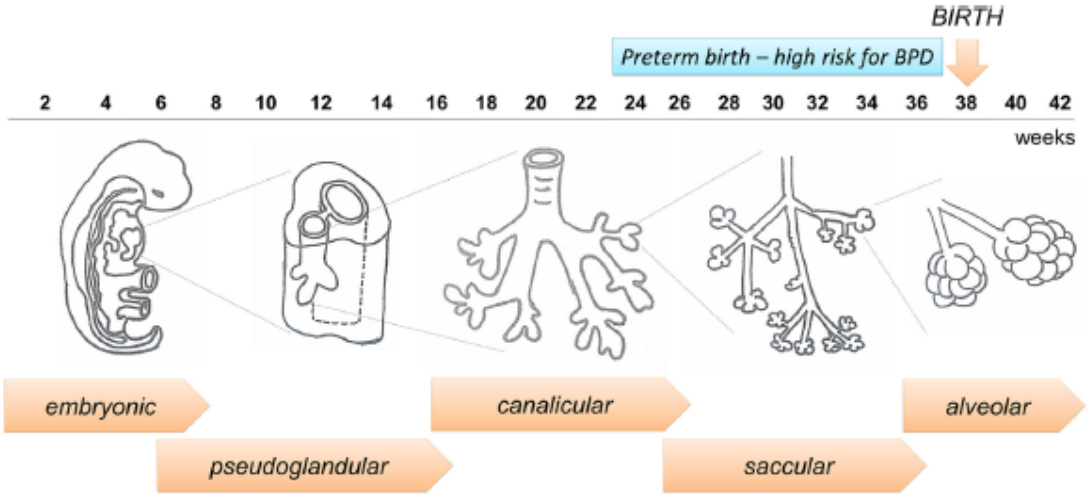

Figure 1: Five Stages of Fetal Lung Development (Adapted from Rivera et al, 2016)

Between 17- and 27-weeks' gestation, the canalicular stage begins and respiratory airways form. The epithelium thins to form the blood-gas barrier and the differentiation of epithelial cells into type I and II pneumocytes occurs. Production of surfactant, a complex lipoprotein, is initiated by type II pneumocytes.[7,33] Surfactant maturation continues into the saccular stage, which occurs between 24 and 36 weeks' gestation.[7] During this stage, primary septation occurs, in which connective tissue forms thin septa within spaces containing a double capillary layer. Lastly, in the alveolar stage beginning at 36 weeks' gestation, tissue extends from the existing primary septa and further divides them into alveoli to fully complete pulmonary development.

Infants born prior to the saccular and alveolar stages of lung development are at risk for severe respiratory complications, including respiratory distress syndrome and its sequela bronchopulmonary dysplasia.

Pathogenesis

Despite several decades having passed since the discovery of BPD, the pathogenesis of this condition remains complex. The cause of BPD is multifactorial, resulting from insult to small airways and interference with alveolarization.[5] Contributing factors can be separated into pre-, peri-, and postnatal causes (Figure 2).[30] During the pre- and perinatal period, the most significant factors impacting the development of BPD include immaturity of the lung, disruption of surfactant homeostasis, genetic susceptibility, intrauterine and perinatal infections, and lung growth restriction secondary to placenta insufficiency.[30] Recent literature also suggests that preeclampsia alone increases the risk for subsequent development of BPD.[34] Infants with maternal preeclampsia were found to

have higher cord blood levels of fms-like tyrosine kinase 1 (sFlt-1), a protein with antagonistic activity to VEGF, leading to lower levels of VEGF and the subsequent development of BPD.[34] Other prenatal risk factors include chorioamnionitis and prenatal inflammation. Elevated pro-inflammatory cytokine levels such as tumor necrosis factor alpha (TNF-α), Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), Interleukin-8 (IL-8), and C-reactive protein (CRP) in the setting of severe chorioamnionitis is associated with the development of BPD.[34]

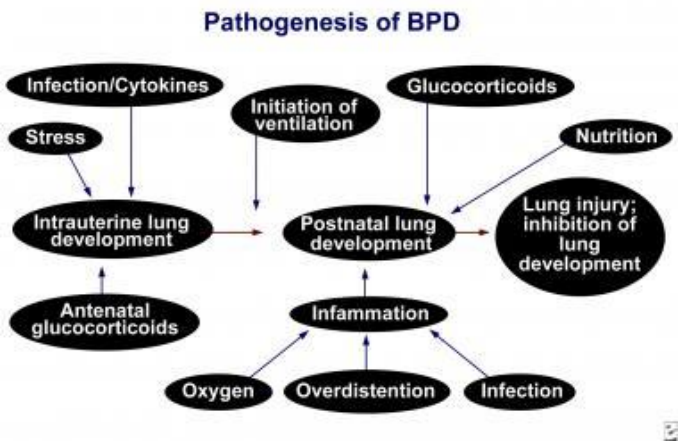

Figure 2: Multifactorial Pathogenesis of Bronchopulmonary Dysplasia[24]

In the postnatal period, mechanical ventilation and supplemental oxygen, though necessary life sustaining treatment, may result in barotrauma and oxidative stress, inducing a pulmonary inflammatory response.[5,30] Even in the absence of chorioamnionitis, elevated levels of pro-inflammatory cytokines have been found in both serum and tracheal aspirates of infants with respiratory distress syndrome or those requiring mechanical ventilation.[34] Specifically, Gien and Kinsella argue that elevated levels of IL-1, IL-6, IL-8, IL-10, and Interferon-gamma (INF-γ) and lower levels of IL-17

are predictive of the development of BPD.[34] Other notable risk factors include male gender, genetic variant of surfactant protein A1 (SP-A1), small size for gestational age (SGA), which is defined as <10th percentile on the Olsen Intrauterine Growth Curves, and high marks on Score for Neonatal Acute Physiology (SNAP).[7,35] SNAP a physiology severity index based on clinical items measured during the first 24 hours of life.[7]

As technology and medical therapy have improved with the utilization of antenatal steroids and noninvasive ventilation strategies, the pathologic findings and clinical course of BPD have also transformed.[5] Although most neonatologists agree that BPD is due to elevated oxygen levels and extended time on ventilation, research suggests that a "new" physiological definition of BPD should include the arrest of lung development rather than simply lung injury.[5,7,36] BPD was formerly defined as causing epithelial damage, atelectasis, smooth muscle hyperplasia with areas of over-inflation, thickening and fibrosis of the alveolar septae, and necrotic and inflammatory changes in the bronchial and bronchiolar mucosa.[7,26,36] Alternatively, BPD is now defined by the arrest of lung development and inflammation with accompanying pro-inflammatory cytokine response and fibrosis.[7]

Pathophysiology

While BPD can occur in full term infants, it is most common in extremely preterm and VLBW infants because there is an interruption in lung development at the saccular and alveolar stages.[7] The inefficient alveolar and capillary network, characterized by dysmorphic alveoli and pulmonary vasculature, in addition to various pre-, peri-, and postnatal factors, contributes to disease development and the release of inflammatory

cytokines that ultimately activate cell death in the infantile lungs.[7] While these cytokines are often released in the setting of infection, they may also present in conditions of inflammation associated with mechanical ventilation.

Studies have suggested that a disruption in normal pulmonary vasculature may be a significant component of BPD.[37,38] In one study with animal models, Wilson et al found that hyperoxia-exposed developing lungs showed alterations in both the number and distribution of pulmonary vessels in the distal lung.[37] Not only was there a significant decrease in arterial concentration but there was also muscular hypertrophy of pulmonary arteries and decreased arterial lumen diameter.[37] With continued hyperoxic exposure, this was associated with right ventricular hypertrophy and eventually failure to thrive.[37]

In one study by Bhatt et al, autopsied lungs from infants with BPD were examined at a molecular level and compared to lungs of infants without BPD.[38] The lungs of infants with BPD had decreased expression of platelet and endothelial cell adhesion molecule-1 (PECAM-1) and vascular endothelial growth factor (VEGF), both of which play part in the disruption of pulmonary vascularization.[7,38] PECAM-1, a cell adhesion and signaling receptor expressed on hematopoietic and endothelial cells, promotes endothelial cell migration and in vivo angiogenesis.[39] With the loss of PECAM-1 function, postnatal lung development is impaired with inhibition of alveolarization and thus, angiogenesis.[38,39]

Similarly, VEGF regulates vasculogenesis, or the differentiation of endothelial cells, as well as angiogenesis.[38] In molecular studies of the developing lung, VEGF is highly expressed in distal airspace epithelial cells, which suggests that this epithelium

may regulate the development of alveolar capillaries.[38,40] Additional studies in mice found that during alveolar development, mRNA levels of VEGF are significantly increased, further supporting this claim.[7] Hyperoxia and inflammatory cytokines, both of which are found in the pathogenesis of BPD, are toxic to endothelial cells, resulting in decreased VEGF expression and, ultimately, impaired vascular growth and alveolar differentiation.[34,38]

Management of Bronchopulmonary Dysplasia

BPD is a complex medical condition without a known cure.[8] Despite recent advancements in treatment and improved outcomes for infants with BPD, there has not been a reduction in the overall incidence of BPD.[7,34] Current treatment of BPD is aimed at not only aiding the survival of the infant but also minimizing further lung damage and promoting physiologic growth to enhance lung development and repair. As the pathogenesis of the disease is multifactorial, treatment approaches are diverse and include both medical treatment and ventilation strategies.[3] While the use of corticosteroids in the treatment and prevention of BPD is the main focus, additional therapies will be briefly discussed below.

Ventilation Strategies

Mechanical ventilation is often necessary life support for infants with RDS but it has been shown to contribute to lung injury and subsequent development of BPD.[41] The incorporation of gentle, non-invasive ventilation strategies in recent years, in addition to

the introduction of antenatal steroids and postnatal surfactant, has resulted in milder pulmonary sequelae with less lung fibrosis and altered the definition of BPD.[3] Replacing pressure-limited ventilation with volume-targeted ventilation has not only reduced the rates of BPD and death but also decreased ventilator-associated inflammation and the duration of ventilation time required.[3,42]

Other preventative techniques used include permissive hypercapnia, early initiation of continuous airway pressure (CPAP), and early extubation attempts for those infants who do require intubation.[3] A meta-analysis by the American Academy of Pediatrics reported that initiation of CPAP at time of birth resulted in lower rates of BPD when compared to prophylactic or early surfactant therapy, while infants were not at an increased risk of adverse outcomes from delaying the administration of surfactant.[43] Based on these findings, the American Academy of Pediatrics (AAP) recommends initial treatment with CPAP for all patients with RDS and intubation and surfactant administration only for those who demonstrate persistent severe respiratory distress, as defined by apnea or a fraction of inspired oxygen (FiO2) of 0.40 or higher.[43]

In addition to ventilation strategies, there have been extensive efforts to determine optimal oxygen saturation targets for the prevention and treatment of BPD.[3] Several studies worldwide have compared low saturation (85%-89%) and high saturation (91%-95%) on the subsequent outcome of BPD. However, despite multiple studies, the optimal saturation target that balances risk of mortality and minimizes the risk of BPD remains unclear.[44–46]

Other Pharmacological Therapies

Pharmacological interventions for BPD include thiazide and loop diuretics, as well as more novel therapies including caffeine, bronchodilators, vitamin A, and inhaled nitric oxide.[3,5] Diuretic therapy has been found to improve short-term pulmonary outcomes, though there is no evidence that it has had an effect on long-term clinical outcomes of infants with BPD. However, with diuretic therapy it is important to monitor for adverse effects, including hypokalemia, alkalosis, hyponatremia, and volume contraction.[5] Caffeine therapy is routinely used in the prevention of BPD, however vitamin A has recently fallen out of use due to prolonged shortages.[5,47]

Corticosteroids

Corticosteroids are a type of steroid hormone produced by the adrenal cortex, specifically in the zona glomerulosa and zona fasciculata.[48] Corticosteroids can be further divided into glucocorticoids and mineralocorticoids and play an active role in a wide variety of physiological processes.[48] Most pertinent to BPD are the role corticosteroids play in reducing inflammation, as well as in the maturation of fetal organs during gestation.[48]

Prenatal corticosteroids have been used for decades with the first randomized controlled trial (RCT) of betamethasone conducted in 1972 by Liggins and Howie.[49] Given prenatally, exogenous corticosteroids have been found to enhance the maturation process of the pulmonary system and stimulate surfactant production in the lungs.[48,50] This subsequently improves respiratory function after birth and reduces the incidence of RDS and BPD.[48,50] Specifically, Liggins and Howie found that the incidence of RDS for infants treated prenatally with betamethasone was 9.0%, while the incidence in the

untreated group was 25.8%.[49] For this reason, the American College of Obstetricians and Gynecologists recommends a single course of corticosteroids for pregnant women between 24 0/7 weeks and 33 6/7 weeks gestation who are at risk of preterm delivery within 7 days.[51]

Postnatal Corticosteroids

By reducing inflammation in the lungs, postnatal corticosteroids have been proven to facilitate extubation and reduce the incidence of BPD in preterm infants.[3] Corticosteroids were first utilized in neonatal medicine in the 1970s, when hydrocortisone was unsuccessfully used in attempt to modify the course of RDS.[52] Later, in the 1980s, two small randomized controlled trials studied high dose dexamethasone (0.5 mg/kg/day) in infants with severe BPD and prolonged ventilator use.[53,54] Both studies noted a statistically significant improvement in lung compliance and ability to be weaned from the ventilator in those who had been treated with dexamethasone.[53,54] In fact, the difference in pulmonary outcomes was so substantial between the dexamethasone and control groups that both studies were terminated early.[53,54] Although these studies found an increased rate of infection among those who were treated with steroids, other adverse effects of the treatment were not reported.[54] Meta-analyses of randomized controlled trials confirmed the initial finding that dexamethasone reduced the rates of BPD and facilitated extubation, while the associated adverse effects (hypertension, hyperglycemia, stunting of growth) were not considered to outweigh the benefits of steroids treatment and were found to be reversible after cessation of treatment.[55]

In a follow-up study performed in 1998, researchers found that at two years of age, although the control group had higher rates of upper respiratory infection and rehospitalization secondary to respiratory problems, the dexamethasone group had a significantly increased incidence of neuro-motor dysfunction and somatic growth impairment.[56] Furthermore, Shinwell et al found that a three day course of dexamethasone initiated within the first 12 hours of life to infants with RDS was associated with a significantly increased incidence of cerebral palsy.[9] Given the double-blind design, adequate sample size, and uniform populations, these studies were considered generalizable and thus, in 2002, the AAP published guidelines recommending against the routine use of systemic steroids in the prevention of BPD.[9–11,56] Rather, the AAP argued its use should be limited to "exceptional clinical circumstances," such as infants who are on maximum oxygen support or unable to be extubated.[11] In these complex clinical circumstances, the clinical team and parents were advised to together discuss the known short- and long-term risks and agree on a treatment plan.[11]

Timing of Dexamethasone Administration

While the use of dexamethasone postnatally decreased after the publications of the AAP recommendations, the incidence and severity of BPD was reported to have increased.[57] Since then, studies reporting the long-term follow up on infants treated with corticosteroids have been published to further investigate the appropriateness of the AAP's recommendations.[57,58] A Cochrane Review in 2010 examined 28 RCTs enrolling a total of 3740 infants who were treated with early postnatal dexamethasone (≤ 7 days of life) and found that, although the administration of early dexamethasone facilitated an

earlier extubation and reduced oxygen requirements at 36 weeks post-menstrual age (PMA), it was associated with increased rates of cerebral palsy and neurological impairment, as well as significant short-term adverse events, including gastrointestinal perforation, gastrointestinal hemorrhage, hyperglycemia, and hypertension.[59] Updates of this review were published in both 2014 and 2017, which again supported the conclusion that the benefits of early dexamethasone use may not outweigh the potential adverse effects.[60,61]

The use of late postnatal dexamethasone (> 8 days of life) was also analyzed in a 2009 Cochrane review, in which 19 RCTs enrolling a total of 1345 infants were reviewed.[62] In contrast to that of early dexamethasone treatment, this analysis concluded that not only was late dexamethasone treatment associated with a lower incidence of BPD at 36 weeks PMA but was also associated with decreased mortality rate at 28 days of life and fewer infants discharged home on oxygen.[62] Follow-up data on 777 infants showed no evidence of differences in major neurosensory disability or the incidence of cerebral palsy.[62] While four studies comprising 200 infants did report increased incidence of abnormal neurological examination, the significance of this finding was unclear and the authors noted several limitations in follow-up, including the lack of power to reliably detect increased rates of long-term neurodevelopmental impairment.[58,62] Updates to this review were published in 2014 and 2017, again both supporting the previous findings.[63,64] Although most of the studies evaluated in the 2009 Cochrane review were randomized, double-blind trials, the methodological quality of the long-term neurological follow-up is variable.[62] It should be noted that some of the studies reporting cerebral palsy as an

outcome did so before five years of age, an age at which the diagnosis of cerebral palsy cannot yet be certain.[62,65] In addition to this, no study was sufficiently powered to detect clinically significant differences in long-term neurosensory outcomes.[62] Given these findings, the AAP revised its previous guidelines and recommended that while early postnatal corticosteroid use be avoided, late postnatal corticosteroid use could be considered in high risk infants with severe disease and those who cannot be weaned from mechanical ventilation.[57]

Dose and Duration of Dexamethasone Administration

Most recent studies used high dexamethasone doses of 0.5 to 1.0 mg/kg/day in various durations ranging from 3 to 42 days.[58,66] It was postulated that perhaps the high dosage and long duration of corticosteroid treatment may be responsible for the poor neurodevelopmental outcomes and that a lower dose for a shorter duration may be associated with less adverse effects.[66] The DART study (Dexamethasone: A Randomized Trial) analyzed the effects of short-term low-dose dexamethasone, defined as a 0.15 mg/kg/day dose tapered over a 10 day period for a cumulative 0.89 mg/kg exposure.[67] Although the study was terminated early due to difficulty enrolling eligible participants, they found that low-dose dexamethasone treatment after the first week of life not only decreased the duration of intubation in ventilator-dependent, very preterm/extremely low birth weight infants but also did not have any associated adverse outcomes.[67] The limited two year follow-up showed no evidence for differences in outcomes, including mortality rate and incidence of cerebral palsy or major neurologic disabilities.[68] While the AAP regarded the DART study as having insufficient evidence to make a recommendation for

or against the use of low dose dexamethasone, this protocol has been adopted by clinical teams in NICUs worldwide for patients who are deemed high risk of developing BPD.[57]

Considerations for High Risk Classification

Available data regarding postnatal steroids have been determined inconclusive and it is recommended that they be reserved for infants who are considered "high risk" of developing BPD or are unable to be weaned off ventilation.[66] However, it remains unclear which clinical characteristics and diagnoses merit the designation of "high risk" and, for this reason, clinical practices vary substantially from hospital to hospital.[3]

While it is important to acknowledge that postnatal corticosteroids are associated with increased risk of neurodevelopmental impairment, one must also remember that preterm birth itself also increases this risk.[18] Furthermore, BPD, brain injury, and severe retinopathy of prematurity, all of which are common complications of preterm birth, have been found to strongly predict the risk of neurodevelopmental impairment in ELBW infants, as well as risk of death.[69] Thus, clinicians often encounter a dilemma -- neurodevelopmental impairment is a possible outcome regardless of use of postnatal steroids. To assess the risk of steroid use, the medical team must consider additional factors that may predict poor outcome of premature birth.

Neonatal infection, a common complication of prematurity, is also associated with poor clinical outcomes and may predispose an infant to BPD.[18,69] Additionally, as mentioned in *Pathogenesis and Pathophysiology of BPD,* elevated levels of certain pro-inflammatory cytokines are predictive of the development of BPD.[34] Given this,

comorbidities that result in a subsequent systemic inflammatory response, such as NEC and sepsis, may be considered a prominent risk factor in the development of BPD.

Necrotizing Enterocolitis

NEC, characterized by ischemic necrosis of the intestinal mucosa, is one of the most common gastrointestinal emergencies in a preterm infant and a major cause of morbidity and mortality.[70,71] Although the pathophysiology is unclear, it is thought to be secondary to an innate immune response to intestinal microbiota by the neonate's immature intestinal tract.[72] This leads to intestinal inflammation and injury, which then may progress to systemic inflammation, sepsis, organ failure, and death.[72] It has been shown that the diagnosis of NEC is associated with increased levels of pro-inflammatory cytokines including IL-6, IL-8/CXCL8, IL-10, IL-18, CRP, and NT-4.[73]

Sepsis

Sepsis is thought to be the systemic response to infection and is defined as a documented infection in addition to the presence of systemic inflammatory response syndrome (SIRS).[74] Criteria for SIRS diagnosis includes tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min), fever or hypothermia (temperature >38 or <36° C), and leukocytosis, leukopenia, or bandemia (white blood count >1200/mm^3, <4000/mm^3, or bandemia ≥10%).[75,76] As mentioned previously, inflammation is a risk factor for BPD, and thus, given the definition of sepsis, sepsis itself is a risk factor for BPD. Additionally, studies have shown that bacterial sepsis developing at least 3 days after birth is associated with the subsequent development of BPD.[77]

Systemic Inflammation as Elevated Risk Factor

Given the association of NEC and/or sepsis with systemic inflammation and systemic inflammation with the development of BPD, it can be concluded that a comorbid diagnosis of NEC and/or sepsis may further increase a preterm infant's risk for BPD. This may warrant treatment with postnatal corticosteroids in this subset of infants, not only to decrease the risk of BPD, but also to decrease time on ventilation. While these comorbidities are common factors in the clinical decision-making process, there is no evidence that these "high risk" infants truly benefit from the use of postnatal corticosteroids. This gap in the literature is ultimately what prompts the proposed intervention.

METHODS

Study design

The proposed study design is a double-blinded randomized controlled trial comparing the effects of low-dose dexamethasone to placebo on the subsequent development of bronchopulmonary dysplasia in extremely preterm infants. Given the controversial nature of postnatal corticosteroid use, this study aims to help guide clinicians in their decision-making process of whether a preterm infant may benefit from a course of steroids. This study will focus on certain subsets of extremely preterm infants that may be at increased risk of poor outcomes, including those with necrotizing enterocolitis and/or sepsis. The primary outcome of this study is the development of bronchopulmonary dysplasia, as defined as an oxygen requirement at 36 weeks PMA. The secondary outcomes of this study include oxygen requirement, time to extubation, overall length of ventilation, and neurologic status at 18-22 months.

Study population and sampling

The study will be conducted in the neonatal intensive care units of Boston Medical Center (BMC) and Brigham and Women's Hospital (BWH) over a period of 48 months. In order to yield sufficient power, each study arm requires a sample size of 91 infants for a total of 182 infants.[78] This was calculated based on the average prevalence of BPD among extremely preterm infants (40%), alpha (α) value of 0.05, a 1:1 allocation to each study arm, beta (β) value of 0.20, and a relative risk of 0.5 for BPD among infants given postnatal corticosteroids.[3] Given that some mothers may opt to seek pediatric care outside

of the BMC and BWH networks, around 10% are expected to be lost to follow up. The sample size will be adjusted to a total of 200 infants in order to account for the anticipated loss to follow up.

Eligible participants will include extremely preterm infants diagnosed with sepsis and/or NEC that require reintubation for management and remain ventilated after 3-5 days. The diagnosis of neonatal sepsis will be made by the finding of culture-proven bloodstream infection with pathogenic bacteria and clinical signs and symptoms. As false negative results are not uncommon in the preterm neonate, the clinical diagnosis of "probable sepsis" at the discretion of the treating team will also be included.[79] Infants who qualify for the NEC subset must be diagnosed with Stage II or Stage III NEC based on the modified Bell Staging Criteria.[70] There are no baseline values for oxygen or ventilator requirements. Infants with prior steroid therapy in the first week after birth, as well as those with congenital neurological defects, are to be excluded from the study.

Intervention

Participants will be randomly stratified into treatment groups using a computer-generated system that will be independent of all investigators, except for the statistician. The allocation will be a 1:1 ratio for treatment to control groups. After written informed consent is obtained from the parent or legal guardian, infants will be randomly allocated to receive twice-daily doses of either a 10-day tapering course of dexamethasone sodium phosphate or an equivalent volume of 0.9% saline placebo. As the DART trial is the protocol of choice in the BMC NICU, the researcher will utilize this protocol for the

means of the study. Following the DART protocol, the 10-day taper of dexamethasone sodium phosphate will be comprised of 0.15 mg/kg/day for 3 days, 0.10 mg/kg/day for 3 days, 0.05 mg/kg/day for 2 days, and 0.02 mg/kg/day for 2 days, for a total of 0.89 mg/kg over the course of 10 days.[67]

Study variables and measures

Baseline demographic and medical information will be collected from mothers upon enrollment and will be supplemented by existing data in the BMC and BWH electronic medical record (EMR) (Tables 4 and 5). Additionally, size for gestational age will be plotted on the Olsen Intrauterine Growth curve using gestational age, birth weight, length, and head circumference.

Table 4: Maternal Demographic Information to be Collected

Maternal age at delivery
Race/ethnicity
Gravida and parity
Smoking status during pregnancy
Preeclampsia
Chorioamnionitis
Prenatal steroids
Cesarean delivery

Table 5: Infant Medical Information to be Collected

Sex
Gestational age
Birth weight, length, head circumference
Multiple birth
Apgar scores at 1 and 5 minutes
Intubated in delivery room
Length of initial intubation, days
Surfactant administration

Ventilator settings, oxygen requirements, and weight will be recorded for all infants at time of enrollment and daily until time of extubation. Overall length of time on ventilation, and oxygen and ventilator requirements from enrollment until 36 weeks PMA will be recorded. Presence of BPD diagnosis will be recorded at 36 weeks PMA. Diagnosis will be based on oxygen requirement at 36 weeks PMA. The severity of BPD will be assessed by amount of supplemental oxygen required at 36 weeks PMA with moderate BPD requiring < 30% oxygen and severe BPD requiring ≥ 30% oxygen and/or CPAP. Neurologic outcomes will be measured using the Hammersmith Infant Neurological Examination (HINE) score.[80] The HINE scoring system was selected because it is a well-studied neurological assessment, is easily performed without associated costs, and has proven to be reliable and precise.[81] The HINE includes 26 items that assess cranial nerve function, posture, muscle tone and movement, reflexes and reactions.[81] A HINE score below 40 will indicate severe motor impairment, scores between 41 and 60 will indicate moderate impairment, and scores above 60 will indicate normal neurologic outcome.[82] A standardized form will be developed in Epic for the HINE with drop down menus to score each of the 26 items.[81] In order to ensure accuracy

and appropriate use of the HINE scoring system, staff pediatricians will be asked to participate in a brief online training module regarding the aspects of the exam.

Recruitment

To facilitate the accrual of participants into the study, NICU clinicians will be informed of the study, including its inclusion/exclusion criteria, intervention, and outcomes. Research personnel will make certain to continuously update clinical staff with protocol changes and any suspensions on recruitment. Research personnel will also play an active role in reminding clinicians of the available study and ensuring all potential candidates are identified and screened for enrollment.

Clinicians will be asked to notify research staff when they have identified potential candidates. The clinicians will inform the infant's parent or legal guardian of the study and, if interested, will request the research assistant to provide detailed information and obtain signed informed consent. Anticipated recruitment time is approximately 48 months, given that BMC and BWH report treating a combined 126 extremely preterm infants each year with an average of 50 infants who acquire NEC and/or sepsis.[47]

Data collection

The majority of the data will be collected by EMR extraction and supplemented by mother or clinician as needed. Baseline data, including maternal demographics and infant medical data, will be extracted from EMR by trained professional research assistants. Day of life of extubation, as well overall length of time on ventilation, will be extracted

from the procedures note in EMR. Ventilator settings and oxygen supplementation will be recorded by nursing staff every shift change as per standard of care, whereas weight will be recorded daily. Oxygen and ventilator requirements at 36 weeks PMA will be recorded using EMR. The diagnosis and severity of bronchopulmonary dysplasia will be extracted from EMR based on oxygen requirement at 36 weeks PMA with moderate BPD requiring <30% oxygen and severe BPD requiring ≥30% oxygen and/or CPAP.

Upon discharge, research personnel will confirm that each infant is scheduled for an 18- to 22-month follow-up visit with a staff pediatrician. At time of visit, the pediatrician will perform a neonatal assessment including both standard of care and research aspects. Clinicians will be asked to fill out the HINE assessment form in Epic. In the visit note, clinicians will be asked to include a provided Epic dot-phrase that will be curated specifically for this research study. The dot-phrase will contain all the clinical and medical information needed for follow-up, oxygen supplementation, occurrence of respiratory illnesses, and hospital readmissions. A summary assessment from the HINE form will automatically be extracted and placed into the dot-phrase note. Patients who are lost to follow up will not be excluded from primary analysis.

Data Analysis

Upon completion of data collection, participants' data will be entered into a statistical computing program. A professional statistician will be consulted to perform all data analysis. Univariate analysis of individual differences in maternal demographic data and baseline infant characteristics will be assessed for all study subjects. The dataset will be

analyzed for differences between the intervention and control groups by study aims as described below.

Aim 1: To determine whether the use of postnatal dexamethasone decreases the risk of developing BPD in infants with a concomitant diagnosis of necrotizing enterocolitis and/or sepsis.

The prevalence of BPD, defined as an oxygen requirement at 36 weeks PMA, will be compared between dexamethasone-treated and non-dexamethasone-treated infants using a chi-square test. Among those who are diagnosed with BPD at 36 weeks PMA in each arm, the severity will be compared using a chi-square test. A further stratified analysis will be performed to determine the individual significance among those with comorbid NEC and/or sepsis.

Aim 2: To compare the effects of low-dose dexamethasone treatment on length of time on ventilation and supplemental oxygen requirement

The unpaired t test will be used to compare the length of time on ventilation after diagnosis of necrotizing enterocolitis and/or sepsis, recorded in hours, for infants in each of the two study arms, as well as the percentage of supplemental oxygen required at 36 weeks PMA.

Aim 3: To determine if low-dose dexamethasone is associated with neurodevelopmental impairment at 18 to 22 months of age

Neurological outcomes at 18 to 22 months of age, as assessed by HINE score and categorized as normal, moderate impairment, and severe impairment, will be compared using a chi-square test.

Timeline and Resources

Based on calculated sample size and 18-month follow-up period, projected date of completion and submission of publication of this study is October 2024, approximately 60 months after study initiation (Table 6).

Table 6: Projected Timeline

July 2019 – September 2019	- IRB submission and approval
October 2019 – October 2023	- Recruitment of participants - Data collection, EMR data extraction
November 2023 – April 2024	- Completion of recruitment - Continue with data collection and EMR extraction
April 2024 – August 2024	- Completion of data collection - Data consolidation and analysis
August 2024 – October 2024	- Completion of data analysis - Preparation and submission of publication

Resources for this study include administrative support, clinical support, and logistical supplies (Table 7). This includes clinical research assistants and primary investigators at both BMC and BWH, and a statistician for data analysis. The support of pediatric staff is necessary for proficient follow-up during the 18- to 22-month outpatient visit. Logistical supplies include IRB approval, paperwork for the consenting process, an electronic data collection software, and statistical analysis software.

Table 7: Resources

Administrative Support - Clinical research assistants - Primary investigator and co-investigator - Statistician
Clinical Support - Pediatric consultation
Logistical Supplies - IRB approval - Paperwork for consenting - Electronic data collection software - Statistical software

Institutional Review Board

The study protocol will be submitted to both the BMC and BWH Institutional Review Board for ethical approval. Extremely preterm infants are a high-risk, vulnerable population and, therefore, this study will warrant full board review to protect the human participants.

CONCLUSION

Discussion

Despite an abundance of research on the role of postnatal dexamethasone in its prevention of BPD, current guidelines continue to recommend its use exclusively in high risk infants.[57] However, researchers have not explored identifying individual characteristics of infants that benefit most from the use of postnatal steroids. For example, infants with NEC and/or sepsis who require reintubation are often administered dexamethasone, however, there is no evidence that these infants truly benefit from a decreased incidence of BPD at 36 weeks PMA. This study is designed to address these current gaps in literature. Strengths of this study include a randomized, double-blinded design and large sample size from a medically and socioeconomically diverse sample of patients, making it generalizable to the United States population at large.

The proposed intervention of this study is adapted from the well-known DART trial, which is used clinically by neonatologists at BMC. It is important to acknowledge that the DART trial experienced recruitment difficulty and was stopped early with a total of 70 patients, despite a calculated sample size of 814.[67] Though it is unclear why they encountered recruitment difficulties, this must be considered a potential obstacle to the completion of the proposed study. Should enrollment be an issue, it is possible to consider extending the length of recruitment or opening enrollment to neighboring hospitals, such as Tufts Medical Center and St. Elizabeth's Medical Center.

The analysis of neurodevelopmental outcomes is another anticipated obstacle in this study. While literature indicates that postnatal dexamethasone increases the incidence

of neurodevelopmental impairment and cerebral palsy, premature birth and BPD in general are also known to be associated with increased incidences.[9,29] Thus, the differentiation between these associations may be difficult to assess. Additionally, similar to previous studies, it is possible that this study may be underpowered to detect significant differences in neurological outcomes.[62]

Summary

Optimal prevention and treatment of BPD has not been established, despite recent advances in medical research and technology, such as non-invasive ventilation techniques and the use of exogenous surfactant. Postnatal corticosteroid use has been a topic of interest in neonatal research for several years. Despite apparent benefits of dexamethasone in preventing BPD, its use remains controversial as it is difficult to ascertain whether its benefits outweigh the increased risk of neurodevelopmental impairment. The AAP continues to recommend against routine use of postnatal steroids and instead advises the consideration of its use only in very high-risk infants.[57]

There is currently no literature on which subsets of high-risk infants warrant and benefit from the use of postnatal steroids and, as a result, clinical practice varies widely. As dexamethasone has been proven to prevent the development of BPD, the investigation of which subsets of preterm infants should receive treatment warrants further study. This proposed study will investigate a 10-day taper of low-dose dexamethasone in infants with NEC and/or sepsis, who require reintubation for management and its effects on the

subsequent diagnosis of BPD, in hopes that it will identify a subset of high-risk infants whose benefits of steroid use outweigh its risks.

Clinical and public health significance

Preterm birth, affecting 1 in 10 infants in the United States, is an outstanding burden medically and financially, both to the parents and the healthcare system.[1] BPD is one of the most common and significant adverse effects of preterm birth and, although not yet curable, it is preventable not only with non-invasive ventilatory strategies but also with the use of corticosteroids pre- and post-natally.[25]

The results of this proposed study will build the evidence base for the use of postnatal steroids in the prevention of BPD in extremely preterm infants. This will help to establish a more detailed characterization of infants for whom the benefits of steroids outweigh the risks. The results will enable clinicians to make more informed decisions regarding the medical care of extremely preterm infants and more accurately counsel parents on the incidence of subsequent BPD development, as well as long-term morbidities. Ultimately, the goal for the proposed study is to provide data to support optimal and comprehensive care for this vulnerable population of extremely preterm infants.

LIST OF JOURNAL ABBREVIATIONS

Adv Neonatal Care	Advances in Neonatal Care
Am J Respir Cell Mol Biol	American Journal of Respiratory Cell and Molecular Biology
Am J Respir Crit Care Med	American Journal of Respiratory and Critical Care Medicine
Anesth Analg	Anesthesia and Analgesia
Arch Dis Child Fetal Neonatal Ed	Archives of Disease in Childhood. Fetal and Neonatal Edition
BMJ	British Medical Journal
BMJ Clin Evid	British Medical Journal Clinical Evidence
Curr Opin Pediatr	Current Opinion in Pediatrics
Cochrane Database Syst Rev	Cochrane Database System Review
Fertil Steril	Fertility and Sterility
Front Med	Frontiers in Medicine
Front Pediatr	Frontiers in Pediatrics
Int J Gen Med	International Journal of General Medicine
Int J Pediatr	International Journal of Pediatrics
JAMA	Journal of the American Medical Association
J Biol Chem	Journal of Biological Chemistry
J Clin Med	Journal of Clinical Medicine

J Matern Fetal Neonatal Med	Journal of Maternal-Fetal Neonatal Medicine
J Perinatol	Journal of Perinatology
Mol Cell Pediatr	Molecular and Cellular Pediatrics
N Engl J Med	New England Journal Medicine
Pediatr Neurol	Pediatric Neurology
Pediatr Res	Pediatric Research
Semin Fetal Neonatal Med	Seminars in Fetal and Neonatal Medicine
Semin Perinatol	Seminars in Perinatology

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