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Factors associated with the response to postnatal dexamethasone use in very low birthweight infants: a nationwide cohort study

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ABSTRACT

Background Dexamethasone is widely used as a systemic corticosteroid to treat and prevent bronchopulmonary dysplasia (BPD) in preterm infants. We evaluated the current epidemiology of dexamethasone use to prevent BPD and analyse the factors associated with the response to dexamethasone in very low birthweight infants using a nationwide database.

Methods We included very low birthweight infants born between January 2013 and December 2020 with a gestational age of 23–31 weeks using data from the Korean Neonatal Network registry. Patients were grouped based on their dexamethasone use into 'Dex' or 'No Dex' groups. Clinical variables and data were collected, and the annual trends of dexamethasone use and the proportion of patients who received dexamethasone according to gestational age were analysed. Respiratory outcomes were compared between the groups. Univariate and multivariate analyses were performed to analyse factors associated with the response to dexamethasone in BPD.

Results Of 11 261 eligible infants, 2313 (20.5%) received dexamethasone, and 1714 (74.1%) of them were diagnosed with moderate-to-severe BPD. The 8-year annual prevalence of dexamethasone use was 17.7–22.3%. The 'Dex' group had more moderate-to-severe BPD, more frequent invasive ventilation use at a postmenstrual age of 36 weeks and longer ventilator duration. Birth weight, 5-minute APGAR score, pulmonary hypertension within the first 28 days, surgical treatment of patent ductus arteriosus, medical treatment of patent ductus arteriosus, pathological chorioamnionitis, hydrocortisone or budesonide use, surgical management of necrotising enterocolitis and fungal sepsis were associated with BPD after dexamethasone use.

Conclusions Approximately 20.5% of preterm infants received dexamethasone, and the frequency increased as gestational age decreased. Poor response to dexamethasone was associated with antenatal and postnatal inflammation, low birth weight and early pulmonary hypertension.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Dexamethasone is used as a systemic corticosteroid to treat and prevent bronchopulmonary dysplasia in preterm infants.

WHAT THIS STUDY ADDS

⇒ Antenatal and postnatal inflammation, low birth weight and early pulmonary hypertension affect the responsiveness to dexamethasone administration.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research must include the causal relationship between clinical factors and dexamethasone with detailed data.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects premature infants and is caused by impaired lung development and damage. It is one of the most common complications of prematurity, with a variable incidence ranging from 11% to 50% depending on the gestational age, birth weight of the cohort and definition of BPD.[1] In Korea, the recent annual report of the Korean Neonatal Network (KNN) indicates that moderate-to-severe BPD was diagnosed in 34% of very low birthweight infants (VLBWIs) defined as a weight of less than 1500 g at birth.[2] Despite recent advances in respiratory care that have greatly improved the survival of preterm infants, the prevalence of BPD has not decreased.[3 4]

Corticosteroids, which have potent anti-inflammatory effects, are used postnatally to prevent and treat BPD.[5] Low-dose dexamethasone treatment initiated after the first week of life has been found to facilitate extubation, shorten the duration of intubation and provide long-term benefits in infants at high risk of BPD.[6] However, the response to dexamethasone treatment for the prevention of BPD varies among patients, even among

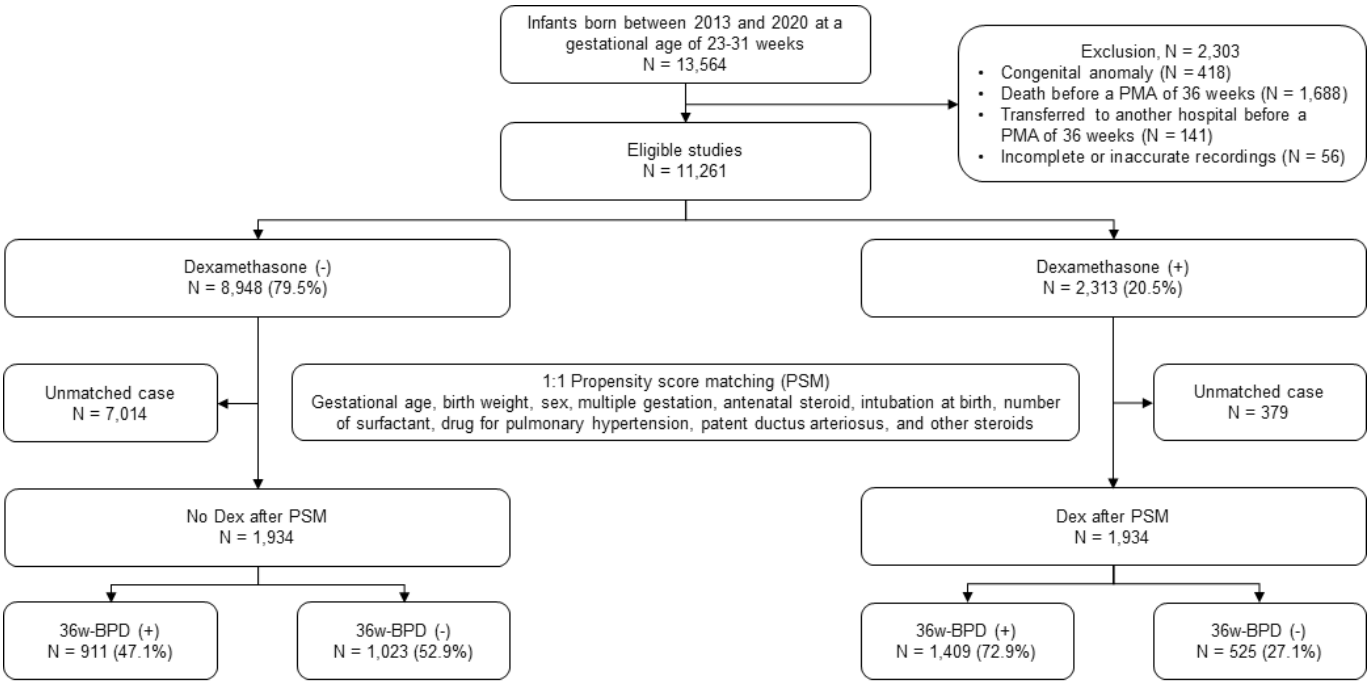

Figure 1. Study population flow chart

Figure 1 Patient flow chart of the study population. BPD, bronchopulmonary dysplasia.

those of the same gestational age or birth weight in the clinical field. Additionally, studies regarding the factors associated with the response to dexamethasone are still lacking.

Therefore, this study aimed to evaluate the current epidemiology of dexamethasone use for the prevention of BPD and to analyse factors associated with the response to dexamethasone in VLBWIs using a nationwide database.

METHODS

Data source and study population

Data from the KNN registry, which is a web-based nationwide cohort database of VLBWIs from 76 neonatal intensive care units, were used. VLBWIs born between January 2013 and December 2020 with a gestational age of 23–31 weeks were included in this study. Patients with congenital anomalies or those who were not available to be diagnosed with BPD due to death, discharge or transferring to other hospitals before 36 weeks of postmenstrual age (PMA) were excluded from the study. The patients were grouped into 'Dex' or 'No Dex' according to dexamethasone use.

Clinical variables and data collection

Maternal risks included diabetes mellitus, hypertension (HTN), preterm premature rupture of membranes (PPROM), antenatal steroid use, oligohydramnios and in vitro fertilisation–embryo transfer. Perinatal and postnatal characteristics included gestational age, birth weight, sex, multiple gestations, delivery mode, as well as appearance, pulse, grimace, activity and respiration (APGAR) scores, small for gestational age, surfactant use, air leak syndrome, pulmonary haemorrhage, patent ductus arteriosus (PDA) treatment, pulmonary HTN (pHTN), intraventricular haemorrhage, periventricular leucomalacia, sepsis, fungal sepsis, necrotising enterocolitis (NEC) and retinopathy of prematurity. Annual trends of dexamethasone use and the proportion of patients receiving dexamethasone according to gestational age were analysed.

Definition of BPD

BPD and its severity were defined based on the 2001 National Institute of Child Health and Human Development consensus; BPD was diagnosed when supplemental oxygen was used for ≥28 days. Mild, moderate or severe BPD was classified depending on the extent of supplemental oxygen or respiratory support.[7] Patients with moderate or severe BPD were categorised as '36w-BPD' in this study.

Definition of respiratory outcomes and response to dexamethasone

The diagnosis of '36w-BPD', mechanical ventilator support at a PMA of 36 weeks and duration of ventilator care were compared between the 'Dex' and 'No Dex' groups. The '36w-BPD' was used as the outcome for the response to dexamethasone when analysing factors associated with the response to dexamethasone.

Statistical analysis

Descriptive statistics were used to show the clinical characteristics of the study population. Data are presented as

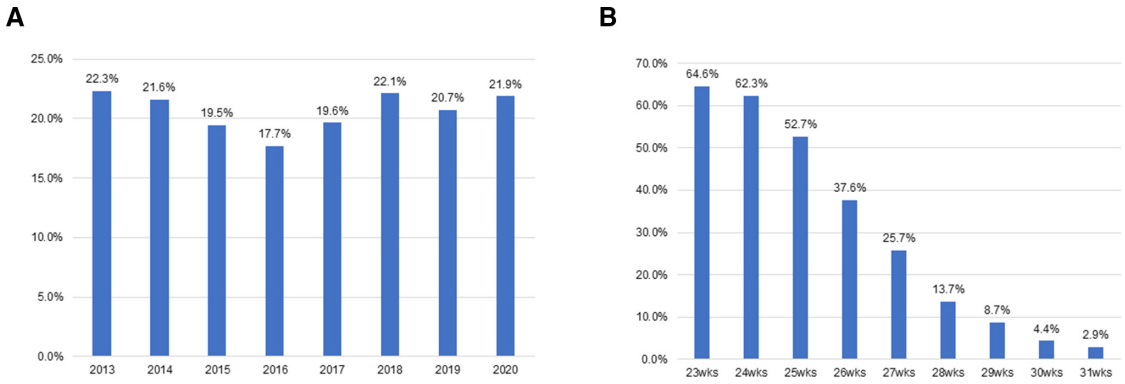

Figure 2 (A) The proportion of infants receiving dexamethasone (annual trends). (B) The proportion of infants receiving dexamethasone in different gestational age groups.

the number of cases (%), mean with SD and median with IQR. The Mann-Whitney U test was used for continuous variables. The X^2 test, or Fisher's exact test, was used for categorical variables. Propensity score matching (PSM) with 1:1 matching was used to balance the 'Dex' and 'No Dex' groups by minimising confounding factors. Covariates used in PSM included gestational age, birth weight, sex, multiple gestations, antenatal steroid use, intubation at birth, number of surfactant doses, drug use for pHTN within the first 28 days, the strategy of PDA treatment and other steroids used for BPD. The greedy nearest neighbour approach was used to select each matched pair. To ensure balanced matches, a calliper set the maximum acceptable difference between the two groups at 0.01, resulting in a relatively narrow difference between the matched groups. The Wilcoxon signed-rank test for continuous variables and the McNemar test for categorical variables were conducted to assess the covariate balance between the groups. To identify factors associated with 36w-BPD outcomes in infants who received dexamethasone, a univariate logistic regression analysis followed by a multivariable regression analysis was performed. All analyses were performed using SAS, V.9.4 (SAS Institute) and the R package, V.4.0.4 (http://www.R-project.org). For all tests, $p<0.05$ was considered significant.

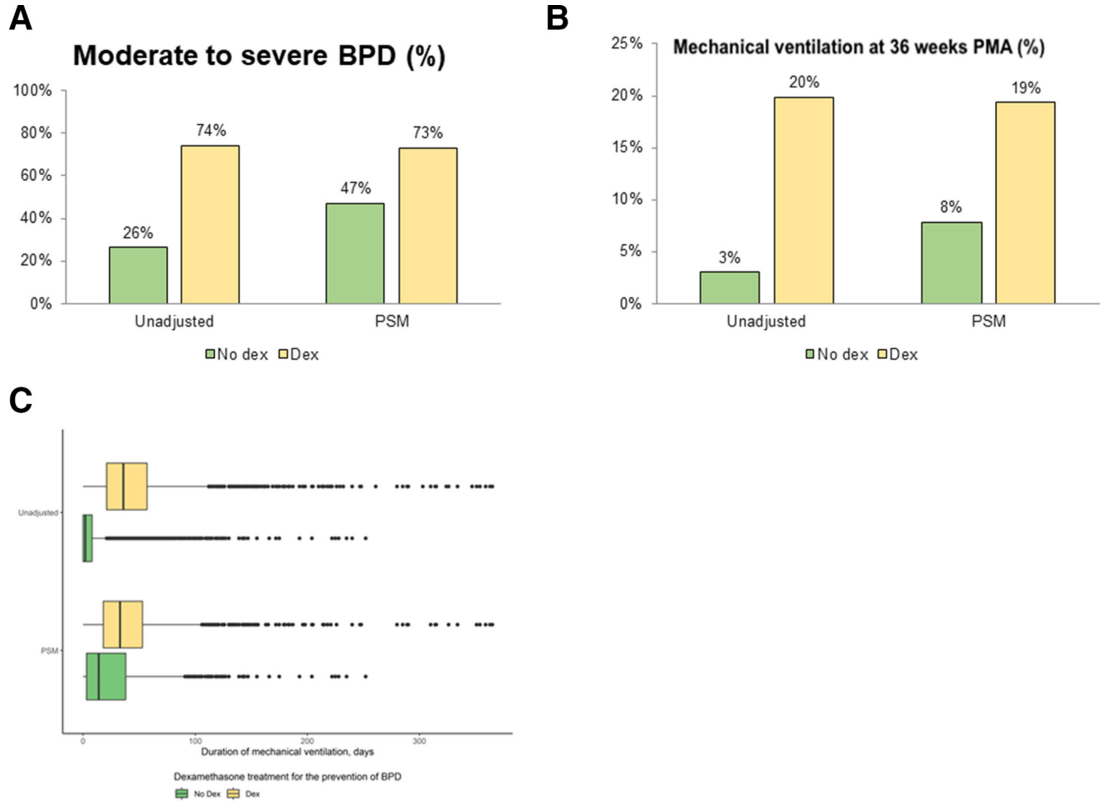

Figure 3 Comparison of respiratory severity between the 'No Dex' and 'Dex' groups before and after propensity score matching (PSM): (A) the prevalence of moderate-to-severe BPD; (B) the proportion of patients with mechanical ventilation at a PMA of 36 weeks; (C) the duration of mechanical ventilator care. BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

Patient and public involvement

Participants were not involved in the design, development of outcome measures or other aspects of the conduct of study.

RESULTS

Study population

The selection process for the study population is shown in figure 1. From January 2013 to December 2020, a total of 13564 infants with gestational ages of 23–31 weeks were registered in KNN. Out of these, 418 infants with congenital anomalies, 1688 infants who died before PMA of 36 weeks, 141 infants who were transferred to another hospital before PMA of 36 weeks and 56 infants with incomplete or inaccurate recordings were excluded. The remaining 11261 infants were eligible for the study. Among these, 2313 (20.5%) infants received dexamethasone, and among the infants who received dexamethasone, 1714 (74.1%) were diagnosed with moderate-to-severe BPD.

Epidemiology of dexamethasone use in VLBWIs

The annual prevalence of dexamethasone use ranged between 17.7% and 22.3%, which did not significantly change over 8 years (figure 2A). Dexamethasone use was more common among patients with a lower gestational age. The proportion of patients receiving dexamethasone was 64.6% for those with a gestational age of 23 weeks, followed by 13.7% for those at 28 weeks and 2.9% for those at 31 weeks (figure 2B). Among patients with a gestational age <28 weeks, 41% were treated with dexamethasone.

Comparison of respiratory outcomes between the 'Dex' and 'No Dex' groups

After PSM, 1934 pairs were categorised into the 'Dex' or 'No Dex' groups. The comparison of clinical characteristics between the two groups before and after PSM is shown in online supplemental table 1. The 'Dex' group had significantly more moderate-to-severe BPD (72.9% vs 47.1%; p<0.0001; figure 3A and table 1) and invasive ventilation use more frequently at a PMA of 36 weeks (19.3% vs 7.9%; p<0.0001; figure 3B and table 1). The median (IQR) duration of ventilator care was 33 (18–53) days in the 'Dex' group, which was significantly longer than in the 'No Dex' group (14 (3–38) days; p<0.0001; figure 3C and table 1).

Factors associated with 36w-BPD outcomes in infants who received dexamethasone

Univariate analysis identified that air leak syndrome, massive pulmonary haemorrhage, pHTN within the first 28 days, surgical ligation of PDA, chorioamnionitis, PPROM for >18 hours, oligohydramnios, hydrocortisone or budesonide use, surgical management of NEC, spontaneous intestinal perforation, and bacterial and fungal sepsis were significantly and positively associated with 36w-BPD. Gestational age, birth weight, 5-minute APGAR score, surfactant use and maternal gestational diabetes mellitus were significantly and negatively associated with 36w-BPD (online supplemental table 2). From multivariable analysis, birth weight, 5-minute APGAR score, pHTN within the first 28 days, surgical treatment of PDA, medical treatment of PDA, pathological chorioamnionitis, hydrocortisone or budesonide use, surgical management of NEC and fungal sepsis were independently associated with 36w-BPD (OR, 1.00, 0.93, 2.58, 1.91, 1.45, 1.34, 1.98, 2.24 and 3.57, respectively; all p<0.05) (table 2).

DISCUSSION

This study used nationwide data from South Korea to identify the epidemiology of dexamethasone use in VLBWIs and to explore the clinical factors associated with the response to dexamethasone. Our aim was to find evidence that could help select candidates for dexamethasone use for the prevention of BPD in clinical practice.

Between 2013 and 2020, the rate of dexamethasone use in preterm infants born at a gestational age of 23–31 weeks was 20.5%, and the annual trend of dexamethasone use did not change throughout the 8 years. The frequency of dexamethasone use increased as patients' gestational age decreased. Approximately 41% of patients with a gestational age of 23–27 weeks received dexamethasone treatment.

Systemic postnatal corticosteroid treatment has been reported to prevent BPD in many studies.[8 9] However, the policy statements for systemic dexamethasone or other corticosteroid use are still cautious, suggesting recommendations for specific regimens or indications.[10]

Table 1 Respiratory outcomes in the 'No Dex' and 'Dex' groups

	Overall population			Propensity score-matched population		
Respiratory outcomes	No Dex (n=8948)	Dex (n=2313)	P value	No Dex (n=1934)	Dex (n=1934)	P value
Moderate-to-severe BPD	2353 (26.3)	1714 (74.1)	<0.0001	911 (47.1)	1409 (72.9)	<0.0001
Mechanical ventilation at a PMA of 36 weeks	269 (3.0)	458 (19.8)	<0.0001	152 (7.9)	374 (19.3)	<0.0001
Duration of invasive ventilation (days)	2 (0–8)	36 (21–57)	<0.0001	14 (3–38)	33 (18–53)	<0.0001

Data are presented as numbers (%) or medians (IQR).
BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

Table 2 Multivariate logistic regression analysis for factors associated with 36w-BPD outcomes in infants who received dexamethasone

	Infants who received dexamethasone (n=2313)		Multivariate analysis		
Variables	**36w-BPD (–) (n=599)**	**36w-BPD (+) (n=1714)**	**OR**	**95% CI**	**P value**
Antenatal characteristics					
GA (weeks)	26.8±1.8	26.5±1.9	1.016	0.999 to 1.033	0.0671
Birth weight (g)	946.5±235.2	855.7±236.1	0.999	0.998 to 1.000	0.0031
SGA (<10th percentile)	36 (6.0)	208 (12.1)	1.745	0.973 to 3.129	0.0616
Maternal DM					
No	531 (88.7)	1582 (92.3)	Ref		
GDM	60 (10.0)	107 (6.2)	0.663	0.434 to 1.012	0.0571
Overt DM	8 (1.3)	25 (1.5)	1.365	0.491 to 3.795	0.5510
Chorioamnionitis	201 (40.0)	698 (47.8)	1.335	1.033 to 1.726	0.0270
PPROM (≥18 hours)	125 (21.7)	471 (29.4)	1.250	0.934 to 1.673	0.1330
Amniotic fluid abnormality					
No	472 (86.8)	1276 (81.9)	Ref		
Oligohydramnios	67 (12.3)	262 (16.8)	1.016	0.702 to 1.470	0.9339
Hydramnios	5 (0.9)	20 (1.3)	1.787	0.476 to 6.702	0.3896
Delivery room management					
5-minute APGAR score	6.6±1.7	6.3±1.7	0.927	0.859 to 1.000	0.0491
Postnatal NICU characteristics					
Surfactant					
Yes	593 (99.0)	1672 (97.5)	Ref		
No	6 (1.0)	42 (2.5)	3.027	0.987 to 9.286	0.0527
Air leak syndrome	33 (5.5)	146 (8.5)	1.273	0.782 to 2.072	0.3309
Massive pulmonary haemorrhage	36 (6.0)	148 (8.6)	0.955	0.587 to 1.554	0.8544
Drug for pHTN within 28 days of birth	22 (3.7)	216 (12.6)	2.578	1.515 to 4.386	0.0005
PDA treatment					
No	249 (42.3)	627 (37.2)	Ref		
Only medication	227 (38.6)	570 (33.9)	1.452	1.107 to 1.905	0.0071
Surgical ligation	112 (19.0)	487 (28.9)	1.910	1.381 to 2.641	<0.0001
Other steroids use	36 (6.3)	208 (13.3)	1.979	1.274 to 3.075	0.0024
Bacterial sepsis	157 (26.2)	665 (38.8)	1.269	0.977 to 1.649	0.0738
Fungal sepsis	6 (1.0)	83 (4.8)	3.569	1.256 to 10.145	0.0170
Surgical management for NEC					
No	567 (94.7)	1522 (88.9)	Ref		
Symptomatic but untreated	18 (3.0)	62 (3.6)	0.730	0.380 to 1.403	0.3454
Yes	14 (2.3)	129 (7.5)	2.238	1.150 to 4.354	0.0177
Spontaneous bowel perforation	15 (2.5)	76 (4.4)	1.154	0.568 to 2.346	0.6916

Data are presented as numbers (%) or mean±SD.
APGAR, appearance, pulse, grimace, activity and respiration; BPD, bronchopulmonary dysplasia; DM, diabetes mellitus; GA, gestational age; GDM, gestational diabetes mellitus; NEC, necrotising enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; pHTN, pulmonary hypertension; PPROM, preterm premature rupture of membranes; Ref, reference; SGA, small for gestational age.

A recent systemic review study revealed that 2–4 mg/kg of dexamethasone use initiated at 8–14 days of life may be the most beneficial for preventing BPD in preterm infants <32 weeks.[11] The previously reported prevalence of postnatal corticosteroid use varies widely, ranging from 3% to 50%.[12 13]

However, the effects of different corticosteroid regimens on outcomes such as mortality, pulmonary morbidity

and long-term neurodevelopmental impairment are not clear.[14] More importantly, if patients receiving corticosteroids are not expected to benefit from the prevention of BPD, the adverse effects become more negligible. Therefore, the selection of appropriate candidates for corticosteroid use is crucial.

Dassios *et al* suggested that more immature infants are less responsive to dexamethasone for preventing BPD when administered after the first week of life.[15] Another small single-centre study showed that maternal chorioamnionitis or intrauterine growth restriction was not associated with the response to hydrocortisone.[16] A Korean single-centre study found that pathological chorioamnionitis and PROM were associated with poor responses to dexamethasone.[17] In our study, we showed that only pathological chorioamnionitis, not PROM or oligohydramnios, was independently associated with a poor response to dexamethasone among antenatal factors. Among postnatal factors, severe inflammation, including surgical NEC and fungal sepsis, was strongly associated with a poor response to dexamethasone. Notably, patients requiring medication for pHTN within 28 days of life had a higher OR of a poor response to dexamethasone than those without pHTN. Low birth weight and a low 5-minute APGAR score were independently associated with 36w-BPD among patients who received dexamethasone. However, low gestational age lost significance after adjustment for other clinical factors.

The 'Dex' group was more likely to be diagnosed with moderate-to-severe BPD, use mechanical ventilation at a PMA of 36 weeks and require longer duration of ventilator care than the 'No Dex' group after PSM. These results are likely due to the intrinsically higher risk of BPD in the 'Dex' group than in the 'No Dex' group, which cannot be shown in detail due to the nature of the nationwide registry of multiple centres with diverse practice protocols.

Inflammation is the key factor explaining the development of BPD. Impaired lung development and injury due to prenatal and postnatal factors that cause inflammation and damage to the highly vulnerable premature lungs lead to BPD.[18] The persistence and non-resolution of lung inflammation alter the lung's ability to repair, contribute to fibrosis and inhibit secondary septation, alveolarisation and normal vascular development. This inflammatory response leads to BPD.[19] Glucocorticoids exert their effects by binding to the glucocorticoid receptor, a ligand-activated transcription factor that both positively and negatively regulates gene expression.[20] Corticosteroids decrease inflammation in the lungs by inhibiting the synthesis of proinflammatory mediators, including macrophages, eosinophils, lymphocytes, mast cells and dendritic cells, and suppressing phospholipase A2, which is responsible for the production of numerous inflammatory mediators.[21]

Previous studies have suggested that pHTN, PDA, NEC, sepsis and maternal chorioamnionitis are factors associated with BPD.[22–26] These factors may have directly negatively impacted the response to dexamethasone for BPD. It is possible that these factors are risk factors for BPD and therefore appear to influence the response to dexamethasone treatment.

Our study has some limitations. Due to the nature of retrospective cohorts without interventions, a consistent protocol for dexamethasone use was impossible. The timing, duration or cumulative dose of dexamethasone use in each patient is not specified in the KNN registry data format. Therefore, this study is limited in its ability to explain because the linear relationship between postnatal factors such as postnatal infection and dexamethasone administration is not clear. To overcome these limitations, a multicentre, prospective cohort study with well-defined protocols for dexamethasone treatment is necessary.

In Korea, patients who required dexamethasone use had poorer respiratory outcomes at a PMA of 36 weeks in the clinical field. Antenatal and postnatal inflammation, as well as low birth weight and the need for PDA treatment, were associated with a poor response to dexamethasone in preventing BPD. Early pHTN was recently found to be a strong factor associated with the failure of dexamethasone treatment. Further research investigating the causal relationship between clinical factors and dexamethasone with detailed data is warranted.

Contributors SHB—conceptualisation, methodology, formal analysis, writing (original draft), visualisation and revision. JES—conceptualisation, methodology, formal analysis, writing (review and editing) and revision. JH—conceptualisation. IGS—conceptualisation. JP—conceptualisation. SML—conceptualisation. SS—conceptualisation. HSE—conceptualisation. SML—conceptualisation. JL—conceptualisation. SJY—conceptualisation. WC—conceptualisation. MSP—conceptualisation and supervision. All authors approved the final version of the manuscript. MSP is responsible for the overall content as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study protocol was reviewed and approved by the Institutional Review Board of Severance (approval no. 4-2021-0743) and the KNN (2022-014). Written consent was obtained from the parents at each hospital participating in KNN.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. PIs or sub-PIs who belong to organisations participating in the Korean Neonatal Network can access the data. Korean Neonatal Network can be contacted through knn@knn.or.kr.

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