September 20th, 2023 15:00 - 17:00

PARALLEL SESSION 7 - LUNG 2

ID 801. ISOLATED CHRONIC FETAL HYPOXEMIA RESULTS IN VASCULAR REMODELING IN FETAL LAMBS MAINTAINED ON EXTEND.

Doctor Maureen Peers De Nieuwburgh[1,2,3,5], Dr. Mallory Hunt[2], Kevin B. Hayes[1], Isabel R. Randazzo[2], Prashant Chandrasekaran[3], Dr. Fréderic Debième[4], Dr. Olivier Danhaive[5], Dr. Marcus G. Davey[6], Dr. Alan W. Flake[1], Dr. J. William Gaynor[2], Dr. David B. Frank[3]

[1]Center for Fetal Research, Children's Hospital Of Philadelphia, Philadelphia, United States, [2]Division of Cardiovascular Surgery, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, USA, [3]Division of Cardiology, Department of Pediatrics, The Children's Hospital of Philadelphia, , Philadelphia, USA, [4]Department of Obstetrics, Saint-Luc University Hospital,Catholic University of Louvain, , Brussels, Belgium, [5]Division of Neonatology, Department of Pediatrics, St-Luc University Hospital, Catholic University of Louvain, , Brussels, Belgium, [6]Vitara Biomedical Inc., Philadelphia, USA

Background: Severe fetal hypoxia has been associated with failed transition of the fetal circulation at birth causing persistent pulmonary hypertension of the newborn. However, animal models have not been able to achieve fetal hypoxia without concurrent reductions in nutritional delivery or increased maternal stress. Consequently, the implications isolated fetal hypoxia on lung development remains unclear.

Method: In this study, we used an EXTra-uterine Environment for Neonatal Development (EXTEND) to artificially reduce oxygen delivery (DO2) to the fetus (DO2=15 mL/min.kg). Preterm fetal lambs (105-110 days GA) were isolated by cesarean section and supported on EXTEND for 7 days reaching canalicular stage of lung development (n=10) in hypoxic (n=5) or normoxic (n=5) condition; or 17 days reaching saccular stage of lung development (n=8) in hypoxic (n=4) or normoxic (n=4) condition. Study of vascular remodeling included vascular and capillary density, neo-muscularization of vessels and medial wall thickness of distal arteries and was assessed through immunohistochemistry and immunofluorescence.

Results: In our study, aberrant vascular remodeling was observed with a significant reduction in the total number of vessels by 37% and capillary density by 7% after 17 days in hypoxic conditions. Arteriolar medial wall thickness was similar for both 7-day normoxic and hypoxic group but increased by 13% after 17 days in hypoxic conditions (P=0.0002). Small distal arteries (20-50 μm in diameter) comprised the most significantly increased medial wall thickness (P=0.03). In addition, vessels showed a 10% increase in partially muscularized vessels after 7 days in hypoxic conditions (P=0.03) with similarly increased trend in partially muscularized vessels after 17 days in hypoxic condition.

Conclusion: These preliminary data show that isolated fetal hypoxia drives vascular remodeling consistent with vasculopathy observed in persistent pulmonary hypertension of the newborn.
Alan W. Flake holds multiple patents related to EXTEND technology and is a Paid Medical Consultant for Vitara Biomedical Inc.
Marcus Davey is listed as inventor on EXTEND device patents.

ID 679. Changing burden of systemic postnatal corticosteroids use in infants born below 28 weeks of gestation in England and Wales from 2011 to 2020

Doctor T'ng Chang Kwok[1], Professor Don Sharkey[1]

[1]Centre of Perinatal Research, University Of Nottingham, Nottingham, United Kingdom

Background

Postnatal corticosteroids (PNCs) are used in premature infants to facilitate extubation and reduce bronchopulmonary dysplasia (BPD). Due to neurotoxicity concerns, their use decreased in the 2000s. Increased exposure (the burden) to PNCs is associated with worse neurodevelopment outcomes. This study aimed to explore changes in the burden of PNCs use across a national population.

Methods

Routinely recorded data were extracted for infants born <28 weeks gestation in England and Wales across two five-year periods (Epoch 1=2011—2015 and Epoch 2=2016—2020). Systemic PNCs use was defined as ⩾three consecutive days of dexamethasone or methylprednisolone and ⩾seven consecutive days of hydrocortisone use. Cumulative PNCs exposure was the total number of days infants received PNCs divided by the neonatal stay duration. PNCs practices across the two epochs were compared using multivariable regression adjusting for case-mix differences and clustering within units. Cumulative exposure was modelled using generalised linear model with logit function and binomial distribution. Missing data was imputed five times using multivariable imputation by chained equation.

Results

Of the 23,166 infants included, 4,400 (19%) infants received PNCs, with 3,531 (15%), 1,187 (5%) and 28 (0.1%) receiving dexamethasone, hydrocortisone and methylprednisolone respectively. Infants in Epoch 2 were more likely to receive PNCs (aOR 1.50, 95% CI 1.30—1.73) with longer cumulative exposure by 4.5% (95% CI 2.2—6.9) than in Epoch 1. PNCs were commenced 6.3 days earlier in Epoch 2, primarily driven by earlier hydrocortisone use. Dexamethasone use increased by 35% in Epoch 2 and commenced 3.5 days earlier than in Epoch 1. Mortality decreased across the two epochs with increasing BPD and more severe Grade 2/3 BPD in survivors (Table 1). By 2020, 492/1866 (26%) infants received PNCs with a median (IQR) cumulative exposure of 16.5% (9.7—37.0) and more survivors had BPD (72%) or severe Grade 2/3 BPD (41%).

Conclusion

Extremely preterm infants are exposed to PNCs at an increasingly earlier age and for a longer duration. These trends are associated with increasing survival but worsening respiratory morbidity especially more severe BPD. As survival improves, we need new, targeted approaches to reduce the severity of respiratory disease which has life–long implications in these infants.

Infant characteristics	Epoch 1 (2011 – 2015) (N = 12,045)	Epoch 2 (2016 – 2020) (N = 11,121)	Treatment effect[1] Odds ratio / Marginal effects of the mean (95% CI)	p value
Birth characteristics				
Gestational age at birth	26^{+1} (24^{+6} – 27^{+0})	26^{+0} (24^{+5} – 27^{+1})		
Birthweight	810 (680 – 960)	805 (660 – 960)		
Male sex, n (%)	6,554 (54)	6,026 (54)		
Antenatal corticosteroids use, n (%)	10,550 (88)	10,062 (90)		
Systemic postnatal corticosteroids				
Dexamethasone / hydrocortisone / methylprednisolone use, n (%)	1,936 (16)	2,464 (22)	1.50 (1.30 – 1.73)	<0.001
Age started (day)	27 (18 – 41)	23 (15 – 35)	-6.3 (-9.1 – -3.5)	<0.001
Cumulative exposure (%)	13 (8 – 24)	15 (9 – 30)	4.5 (2.2 – 6.9)	<0.001
Duration of use (day)	14 (9 – 26)	15 (10 – 27)	2.3 (0.3 – 4.3)	0.02
Length of neonatal stay (day)	122 (101 – 146)	117 (97 – 141)	-7.4 (-11.9 – -3.0)	0.001
Dexamethasone				
Dexamethasone use, n (%)	1,613 (13)	1,918 (17)	1.35 (1.22 – 1.50)	<0.001
Age started (day)	28 (19 – 43)	26 (19 – 38)	-3.5 (-5.7 – -1.4)	0.001
Cumulative exposure (%)	11 (7 – 19)	12 (8 – 21)	1.3 (-0.6 – 3.1)	0.2
Duration of use (day)	12 (8 – 22)	13 (9 – 24)	0.3 (-1.6 – 2.3)	0.7
Length of neonatal stay (day)	122 (103 – 147)	121 (102 – 145)	-3.8 (-7.4 – -0.3)	0.04
Hydrocortisone				
Hydrocortisone use, n (%)	410 (3)	777 (7)	2.03 (1.40 – 2.94)	<0.001
Age started (day)	24 (13 – 42)	13 (2 – 35)	-9.4 (-16.4 – -2.4)	0.009
Cumulative exposure (%)	19 (9 – 34)	19 (11 – 47)	6.7 (1.8 – 11.6)	0.007
Duration of use (day)	17 (11 – 31)	14 (10 – 32)	3.4 (-2.0 – 8.8)	0.2
Length of neonatal stay (day)	122.5 (95 – 154)	111 (73 – 142)	-12.4 (-22.1 – -2.7)	0.01
Methylprednisolone				
Methylprednisolone use, n (%)	10 (0.08)	18 (0.2)	1.73 (1.06 – 2.83)	0.03
Age started (day)	151.5 (131 – 166)	119 (94 – 156)	13 (-62 – 88)	0.7
Cumulative exposure (%)	3 (2 – 8)	4 (3 – 5)	-0.9 (-3.6 – 1.7)	0.5
Duration of use (day)	5 (3 – 9)	6.5 (4 – 9)	-2.0 (-10.9 – 7.0)	0.6
Length of neonatal stay (day)	179.5 (167 – 217)	153.5 (135 – 167)	-3.3 (-106.8 – 100.2)	0.9
Outcome				
Death, n (%)	2.727 (23)	2,293 (21)	0.87 (0.81 – 0.94)	<0.001
Bronchopulmonary dysplasia[2], n (%)	6,282 (68)	6,193 (70)	1.16 (1.04 – 1.30)	0.009
Severe Grade 2/3 bronchopulmonary dysplasia[2], n (%)	3,352 (36)	3,541 (40)	1.20 (1.11 – 1.30)	<0.001

Table 1 Comparison of birth characteristics, postnatal corticosteroids usage and outcomes between Epoch 1 (2011 – 2015) and Epoch 2 (2016 – 2020) after adjustment for case-mix and clustering of infants within units. Data presented as median (interquartile range) unless stated otherwise. OR = odds ratio. MEM = marginal effects of the mean.

[1]Epoch 1 (2011 – 2015) was used as a reference for the treatment effect measures of odds ratio for categorical variables and marginal effects of the mean for continuous variables.

[2]Respiratory outcomes were obtained for infants who survived to neonatal discharge. Severe bronchopulmonary dysplasia was defined using the Grade 2 or 3 BPD definition by Jensen et al 2019, which is respiratory pressure support requirement at 36 weeks postmenstrual age.

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All authors declare no competing interests. TCK received the Action Medical Research training fellowship, supported by the Albert Gubay Foundation, as part of this study.

ID 307. POSTNATAL COLLAGEN VI EXPRESSION IN THE DEVELOPING HUMAN LUNG

Mr Laszlo Markasz[1], Mr Hamid Mobini-Far[1], Mr Richard Sindelar[2]

[1]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden,

[2]Department of Pathology, Uppsala University Hospital, Uppsala, Sweden

Background

Collagen VI (COL6) is primarily localized to the basement membrane (BM) and required for the alveolar structure and maintenance of pulmonary epithelial function. COL6 promotes lung epithelial cell spreading and wound closure. The COL6 network may have a crucial role in alveolar septation since COL6 -/- mice have simplified alveolar structure. Less is known about its role in human lung development. Our aim was to study COL6 expression in preterm infants with different lung maturational and clinical features.

Methods

COL6 expression was studied in 115 lung samples from newborn infants (21–41 weeks' gestational age [wGA]; 0–228 days' postnatal age [dPNA]), and from adult and school child controls, by immunohistochemistry and digital image analysis. The percent of high intensity area in the stained area (HI%) was calculated.

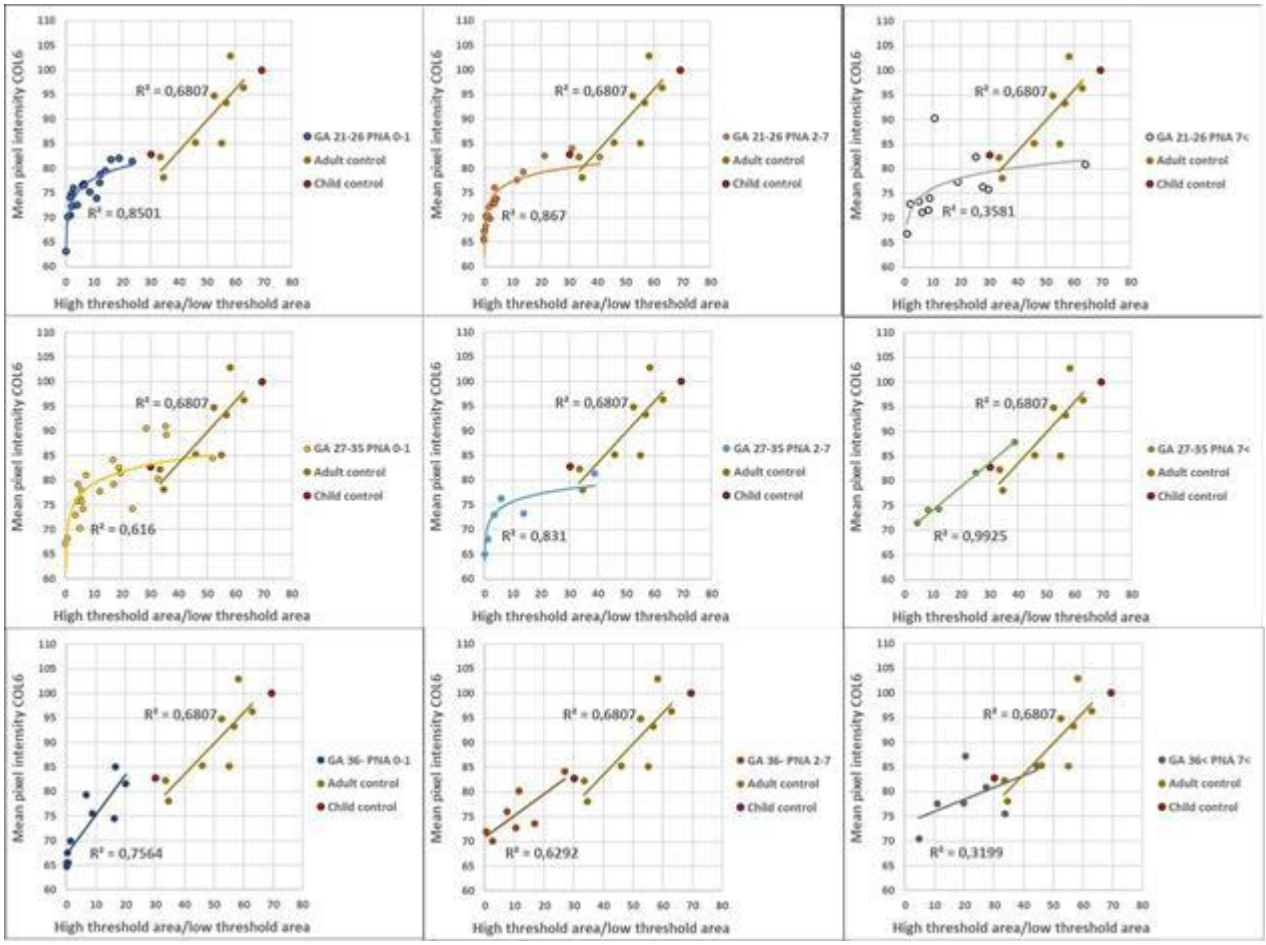
Results

Patients were categorized into groups depending on their GA (21–26; 27–35; >35wGA) and PNA (0–1; 2–7; >7dPNA; Figure 1). The general expression level (mean pixel intensity, MPI) of COL6 varied in all groups. Adults and school children had the highest MPI with a linear correlation to HI%. A levelled logarithmic correlation was found between MPI and HI% in <35wG. The linear correlation corresponded to

homogenously increased COL6 expression in the stained area whereas logarithmic correlation described focal increase of the high intensity areas in the less stained areas. The distribution of COL6 in lung tissue was homogenous in adults, school children and >35wGA, while COL6 expression appeared condensed around air spaces in infants born between 21–26 wGA, but only during 0–7dPNA. After one week of age the distribution became homogenous.

Conclusions

The distribution of COL6 changes during different lung developmental stages and during postnatal life. COL6 seems to be concentrated to epithelial cells at birth during the canalicular stage, with a postnatal spreading into the surrounding mesenchyme. The postnatal reorganizing of COL6 network in the BM of preterms might destabilize the interaction between the epithelium and the extracellular matrix, thereby promoting lung developmental arrest.



None declared

ID 344 POSTNATAL CORTICOSTEROID TREATMENT OF EXTREMELY PRETERM INFANTS IN A TERTIARY PERINATAL CENTRE

Doctor Rachel Morris[1,6], Doctor Kristin Ferguson[1,2], A/Prof David Tingay[1,2,3,4], Doctor Omar Kamlin[1,3,5], Professor Peter Davis[1,3,5], A/Prof Brett Manley[1,3,5]

[1]Newborn Research Centre, The Royal Women's Hospital, Melbourne, Australia, [2]Department of Neonatology, the Royal Children's Hospital, Melbourne, Australia, [3]Neonatal Research, Murdoch Children's Research Institute, Melbourne, Australia, [4]Department of Paediatrics, The University of Melbourne, Melbourne, Australia, [5]Department of Obstetrics and Gynecology, The University of Melbourne, Melbourne, Australia, [6]Department of Neonatology, Singleton Hospital , Swansea, United Kingdom

Background: Bronchopulmonary dysplasia (BPD) is a form of chronic respiratory illness of the very preterm infant associated with increased mortality and morbidity, including worse neurodevelopmental outcomes and respiratory health in childhood. Postnatal systemic corticosteroids are effective in reducing the risk of BPD, but unfortunately associated with short- and long-term side effects, most importantly an increased risk of cerebral palsy. Several postnatal steroid regimens have been proposed over the last 30 years in an attempt to find the optimal balance between benefits and side-effects. The objective of this study was to describe the pattern of use of postnatal dexamethasone for the prevention of BPD in a large perinatal center in the current era.

Methods: A retrospective cohort study of extremely preterm infants (gestational age <28 weeks) born at the Royal Women's Hospital, Melbourne (RWH) between January 2017 and December 2019. Data regarding cumulative dexamethasone dose and duration, ventilation requirements, BPD and death were recorded.

Results: A total of 252 infants were included, of whom 38% received postnatal dexamethasone to prevent BPD. Infants in the steroid–exposed group were more immature than those in the no–steroid group, median (IQR) gestation of 25 (24–26) weeks and 27 (26–27) weeks respectively. In the steroid–exposed group 29% of infants received one standard 10–day dexamethasone course, cumulative dose 0.89mg/kg, as per the regimen used in the Dexamethasone: A Randomized Trial (DART), remaining infants received either further 'DART' courses, the 'Cumming's' regimen (a 42–day weaning course, total cumulative dexamethasone dose of 8.86 mg/kg) or an 'individualized' course. Overall, the median (IQR) cumulative dexamethasone dose given was 1.89 (0.89–3.90) mg/kg with a duration of 20 (10–40) days. A diagnosis of BPD was more common in the steroid–exposed group compared to the no–steroid group (94% vs. 52%) and survival at discharge was lower in the steroid–exposed group (86% vs. 97%).

Conclusion: Approximately one third of extremely preterm infants at RWH receive postnatal steroids. As the coordinating center of the original DART trial, 13 years later, we find that most infants do not receive the standard 10–day DART regimen, rather receiving on average twice the standard total dose.

BM is a co–author on recently updated Cochrane Reviews of 'early' and 'late' postnatal corticosteroids for preterm infants.