The Neonatal Society

Spring Meeting

Royal Society of Medicine, 1 Wimpole Street, London, W1G 0AE

4th March 2021

Meeting Virtual Link: To be emailed to delegates on 3rd March 2021

Session 1: Chair – Professor Helen Budge. Moderator – Professor Lucy Chappell.

10:00. A Aiyengar, Homerton University Hospital
A systematic review of complaints received by neonatal units

10:15. W Alyahya, University of Glasgow
Early feeding with fortified mother's own, donor milk and formula in very preterm infants

10.30. P Clarke, Norfolk and Norwich University Hospital
Vitamin K_1 deficiency in exclusively human milk-fed preterm infants in early infancy

10.45. S Greenbury, Imperial College London
Patterns of postnatal weight gain in very and extremely preterm babies: a 12 year, whole population study

11:00. S Uthaya, Imperial College London
Early versus delayed initiation of parenteral nutrition after very preterm birth

11:15. W Lammons, Imperial College London
Involving parents, patients and clinicians in the design of a UK national double-cluster pragmatic randomised controlled trial

11:30. Tea / coffee

Session 2: Chair – Professor Andy Ewer.

11:45 **Keynote Lecture**
Professor Tim Nawrot, Centre for Environmental Sciences, Hasselt University, Belgium
The impact of pollution on perinatal development

12:45. Lunch break

Session 3: Chair – Professor James Boardman. Moderator – Dr Kevin Goss.

13:45. M Fernandes, University of Southampton
The INTERGROWTH-21st Project International INTER-NDA standards for child development at two years of age: An International Prospective Population-based Study

14:00. A Bonthrone, King's College London
Individual differences in brain development and cognitive outcome in infants with congenital heart disease

14:15. T Hurley, Trinity College Dublin
Melatonin alters systemic cytokine production in neonatal encephalopathy

14:30. V Ponnusamy, Queen Mary University of London
Apoptotic neuronal cell death in neonatal encephalopathy is regulated by the Hippo-YAP-let-7b axis

15:45. S Pregnolato, University of Bristol
Regulation of neuroinflammation and glutamate transport in a term newborn rat model of hypoxic-ischaemic brain injury

15:00. S Williams, Brighton & Sussex Medical School
Assessment of the repeatability and reliability of ultrasound measurement of the new-born corpus callosum and comparison with MRI

15:15. Afternoon Tea / Coffee

Session 4: Chair – Professor Karen Luyt. Moderator – Professor Andy Ewer.

15:30. E Wheater, University of Edinburgh
Association between preterm birth, differential DNA methylation and brain dysmaturation

15:45. O Rivero-Arias, National Perinatal Epidemiology Unit, University of Oxford
Neonatal health care cost of preterm babies born between 27-31 weeks in England: Retrospective analysis of a national birth cohort using the OPTI-PREM dataset

16:00. M Casacão, University College Cork
Early life oxygen dysregulation and gram-positive bacterial challenge in a neonatal rat model induces an inflammatory response but ventilatory control is maintained during normoxia

16:15. N Aiton, Brighton and Sussex University Hospitals NHS Trust
Using 3D photography and imaging analysis to detect prenatal alcohol exposure

16:30. **Prize for best presentation by a trainee**

16:40. **McCance Lecture** – **Introduced by Professor James Boardman, President**
Professor Deborah Lawlor, MRC Integrative Epidemiology Unit, University of Bristol
Early life determinants of cardiometabolic health; separating cause from association

17:40. Close of meeting

Self Certificate of Attendance

A signed electronic version will be emailed to all attendees after the meeting

Neonatal Society Spring Meeting
London
4th March 2019

Name of person claiming CPD points:

(Block letters)…….

Place of Work:…….

Number of CPD points claimed :……
(1 point per hour of attendance – up to a maximum of 10 **CPD Points**)

Claimant's Signature……

Name and signature of Neonatal Society Committee member

……
Howard Clark/Helen Budge/James Boardman/Andrew Ewer/Karen Luyt/Chris Gale/Ela Chakkarapani/Lucy Chappell/Kevin Goss
(please delete as appropriate

Title (Upper case)

A SYSTEMATIC REVIEW OF COMPLAINTS RECEIVED BY NEONATAL UNITS

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Apoorva Aiyengar[1], Tom Morris[1], Kaye Bagshaw[2], Narendra Aladangady[1, 3]

Corresponding author e-mail address: a.aiyengar@nhs.net

Institution(s)

1 Neonatal Unit, Homerton University Hospital NHS Foundation Trust, London, UK
2 Newcomb Library, Homerton University Hospital NHS Foundation Trust, London, UK
3 Child Health, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK

Introduction *(include hypothesis)*

Complaints and/or malpractice claims by family on the care of their babies in the neonatal unit is a pertinent issue. The aim was to review published reports of complaints and/or malpractice claims by family on the care of their babies in the neonatal units in order to understand better the nature of these complaints and the areas of care that they most commonly relate to.

Methods (*include source of funding and ethical approval if required)*

This systematic review was conducted according to PRISMA guidelines.[1] The project protocol was registered with PROSPERO database.[2] *We considered articles in English which report on complaints made by parents/families to neonatal units which were relevant to the clinical care of their baby. We performed our structured search on AMED, CINAHL, EMBASE, EMCARE, SCOPUS and MEDLINE from January 2000 to July 2020.* The articles that reported complaints based on a single patient were excluded.

Results

A total of 352 articles were obtained, with an additional 4 articles from a bibliography and grey literature search. A total of 12 studies were included in our systematic review and analysed.

The most common category of complaint was delay in or incorrect diagnosis. The infants involved in the complaints often had multiple clinical diagnoses. Communication issues were highlighted as a significant category of complaints. The majority of the communication related claims were reported to be between the physicians and family. The factors implicated for clinical staff errors that resulted in parental complaint were lack of clinical and communication training, inadequate supervision of junior staff, work culture and hierarchy resulting in a fear of asking for help, not listening to family concerns and system failure.

Conclusions

Complaints about patient care are often received by neonatal units. Units should be encouraged to share information about such claims as they can correlate to similar clinical issues and can facilitate shared learning. This is to optimise patient outcomes and improve future neonatal unit patients and their families' experience.

References *(include acknowledgement here if appropriate)*

1.Liberati A et al. BMJ. 2009;339:b2700.
2.Aiyengar A, Morris T, Aladangady N. PROSPERO 2020 CRD42020167053

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Prof Narendra Aladangady

Title (Upper case)

EARLY FEEDING WITH FORTIFIED MOTHER'S OWN, DONOR MILK AND FORMULA IN VERY PRETERM INFANTS

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Wesam Alyahya [a, b], PhD, Judith Simpson [c], MD, Ada L. Garcia [a], PhD, Helen Mactier [d], MD, David Young [e], PhD, Christine A. Edwards [a], PhD.

Corresponding author e-mail address: Wesam_y@hotmail.co.uk

Institution(s)

[a] Human Nutrition, School of Medicine, Dentistry and Nursing, Veterinary and Life Sciences, University of Glasgow, UK. [b] Clinical Nutrition, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Saudi Arabia. [c] Neonatal Unit, Royal Hospital for Children, Glasgow, UK. [d] Neonatal Unit, Princess Royal Maternity, Glasgow, UK. [e] Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK

Introduction *(include hypothesis)*

Mother's own milk (MOM) is the optimal feed for premature infants but may not be sufficiently available. Options for alternative feeding include donor human milk (DHM), with or without fortification and preterm formula. This study evaluated the association between early feeding with exclusively/predominantly MOM (PMOM) versus MOM supplemented with fortified-DHM (MDHM) or preterm formula (MF) and in-hospital outcomes.

Methods (*include source of funding and ethical approval if required)*

A multicentre (n=13 units) cohort study including infants born < 32 weeks used data captured at the point of care in Scotland and extracted from the National Neonatal Research Database. Ethical approvals for this study were given by North of Scotland Research Ethics Service (Proportionate Review Research ethics committee approval, Reference: 17/NS/0052) and Health Research Authority approval. Permission from each neonatal unit was obtained.

Results

Data from 1272 infants were analysed. Infants fell into two groups: extremely (EPT) and very preterm infants (VPT), born <28 weeks and 28 - <32 weeks of gestation, respectively. Only 11/365 EPT received formula supplements, precluding useful comparison of MDHM and MF. There was no difference in median (25th -75th centile) growth velocity over the first 30 days of life between PMOM (n= 227) and MDHM (N = 97) groups: 10 (8 – 13) vs. 10 (7 – 13) g/kg/d, p=0.545. For VPT infants, there was similarly no difference in growth velocities between PMOM (n=371), MDHM (N= 187) and MF (N=284): 11 (8 – 14) vs. 11 (8 – 14) vs. 11 (8 – 14) g/kg/day, p >0.05. Cox-regression analysis showed no difference in time to discharge between feeding types nor any difference in major neonatal morbidities.

Conclusions

Feeding with MOM supplemented by fortified DHM compared to preterm formula resulted in comparable short-term growth rates and in-hospital outcomes. Further large clinical trials are needed.

References *(include acknowledgement here if appropriate)*

This study is part of a PhD study and funded by the Royal Embassy of Saudi Arabia Cultural Bureau. We thank Richard Colquhoun and the Neonatal Data Analysis Unit/ Imperial College of London for their advice in achieving ethical approval.

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Dr Helen Mactier.

Title

VITAMIN K_1 DEFICIENCY IN EXCLUSIVELY HUMAN MILK-FED PRETERM INFANTS IN EARLY INFANCY

Authors

Paul Clarke[1,2], David J Card[3], Amy Nichols[1], Vennila Ponnusamy[4], Ajit Mahaveer[5], Kieran Voong[3], Karen Dockery[5], Nicky Holland[4], Shaveta Mulla[1], Lindsay J Hall[6], Cecile Maassen[7], Petra Lux[7], Leon J Schurgers[7], Martin J Shearer[3], Dominic J Harrington[3].

Corresponding author e-mail address: Paul.Clarke@nnuh.nhs.uk

Institutions

1. Neonatal Intensive Care Unit, Norfolk and Norwich University Hospital, Norwich, UK.
2. Norwich Medical School, University of East Anglia, Norwich, UK.
3. Haemostasis & Thrombosis and The Nutristasis Unit, Guy's and St Thomas's Hospital, London, UK.
4. Neonatal Intensive Care Unit, Ashford and St Peter's Hospital, Chertsey, UK.
5. Neonatal Intensive Care Unit, St Mary's Hospital, Manchester, UK.
6. Gut Microbes & Health, Quadram Institute Bioscience, Norwich Research Park, Norwich, UK.
7. Dept. of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht University, The Netherlands.

Introduction

Vitamin K (VK) status of preterm infants post-NICU discharge is unknown. Exclusive breast milk feeding is often the only factor identifiable in idiopathic VK deficiency bleeding. Despite the low VK content of human milk, VK supplements are not routinely given to human milk-fed preterm infants after NICU discharge; in contrast, vitamins A, B, C, and D are widely given. We examined the VK status of breast milk fed preterm infants nearing discharge and in early infancy. Our hypothesis was that, in the absence of post-discharge VK supplementation, exclusively human milk fed preterm infants have a high prevalence of subclinical VK deficiency in early infancy.

Methods

Prospective, multicentre, observational cohort study of preterm infants born <33 weeks' gestation who were exclusively or predominantly human milk fed approaching NICU discharge. We determined VK status by assaying serum concentrations of vitamin K_1 (VK_1), PIVKA-II (undercarboxylated prothrombin), and GluOC (undercarboxylated osteocalcin) as a proportion of total osteocalcin at two time-points: i) pre-discharge for baseline VK status; ii) at ~2-3 months corrected age (CA). Satisfactory VK status was taken as normal PIVKA-II (<51.0 mAU/mL); VK deficiency was taken as raised PIVKA-II (≥51.0 mAU/mL). VK status at ~2-3 months CA was evaluated in relation to feed history. The study had research ethics approval (REC ref. 15/LO/1808).

Results

45 infants recruited in four UK centres underwent assessment of VK status prior to NICU discharge at median PMA 35 (IQR: 34–36) weeks, and 37 completed the study with later assessment at median CA 8 (IQR: 5-14) weeks. Prior to discharge only 1/45 (2%) was VK deficient, the raised PIVKA-II reflecting impaired prothrombin carboxylation. At the follow up visit, 12/37 (32%) remained exclusively breast milk (BM) fed, while 25/37 (68%) were formula milk (FM) or mixed BM-FM fed. Overall by 8 weeks CA, 9/37 (24%) infants had developed VK deficiency: 8/12 (67%) BM-fed were VK deficient vs. only 1/25 (4%) FM/mixed feeding babies, p=0.0001. VK_1 concentrations were significantly lower while PIVKA-II concentrations and GluOC as a proportion of total OC were significantly higher in exclusive BM-fed compared with in FM/mixed fed babies, Table.

Table: Measures of vitamin K status of preterm infants in early infancy according to mode of feeding.

	Exclusive breast milk fed, n=12	Formula/mixed fed, n=25	P-value
Vitamin K_1 (µg/L)*	0.15 (<0.10–0.59)	1.91 (0.16–5.31)	<0.0001
PIVKA-II (mAU/mL)†	80.8 (23.6–496.6)	21.2 (14.1–129.1)	<0.0001
%GluOC of total OC, %	68.8 (37.5-71.1)[a]	7.9 (2.0-43.8)[b]	<0.0001

Data are median (range); *VK_1 non fasting reference range: 0.15-1.55 µg/L. †Normal PIVKA-II is <51.0 mAU/mL. OC, osteocalcin. Total OC = GluOC (undercarboxylated osteocalcin) + GlaOC (carboxylated osteocalcin).
Data available for [a] n=8 infants, [b] n=15 infants. P-values from Mann-Whitney test.

Conclusions

Preterm infants who remain exclusively human milk fed post NICU discharge are at high risk of developing VK deficiency. Routine post-discharge VK_1 supplementation may prevent subclinical VK deficiency in early infancy.

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Title (Upper case)

PATTERNS OF POSTNATAL WEIGHT GAIN IN VERY AND EXTREMELY PRETERM BABIES: A 12 YEAR, WHOLE POPULATION STUDY

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Sam Greenbury, Kayleigh Ougham, Cheryl Battersby, Chris Gale, Sabita Uthaya, Elsa Angelini, Neena Modi

Corresponding author e-mail address: s.greenbury@imperial.ac.uk

Institution(s)

1) Institute for Translational Medicine and Therapeutics Data Science Group, NIHR Imperial Biomedical Research Centre, Imperial College London; 2) Section of Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London; Chelsea and Westminster NHS Foundation Trust, London, UK; 3) Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, UK

Introduction *(include hypothesis)*

Intrauterine and postnatal weight gain are widely regarded as biomarkers of fetal and neonatal wellbeing. However, the optimal pattern of postnatal weight gain following preterm birth is unknown (1). We aimed to estimate changes over time in birth weight and postnatal weight gain in extremely and very preterm babies and explore patterns of postnatal weight gain in relation to major morbidity and healthy survival, hypothesising substantial differences would be identified.

Methods (*include source of funding and ethics approval if required)*

We used whole population data from the UK National Neonatal Research Database for the 12-year period 2008-2019 for infants born below 32 weeks gestational age, admitted to neonatal units in England and Wales. We used Gaussian process regression to model monthly trends, and multilevel regression to estimate unadjusted and adjusted changes in weights and associated z-scores at birth (BW; BWz) and 36 weeks postmenstrual age (PMA) (W36; W36z), and weight loss at age 14 days (ΔW14; ΔW14z). We plotted longitudinal weights for each gestational age category for babies surviving to 36 weeks PMA with and without major morbidities. The study was funded through a MRC grant awarded to Professor Modi and approved by the Health Research Authority, Health and Care Research Wales (IRAS project ID 273001) and all contributing neonatal units (2).

Results

The cohort comprised 90,817 infants. Over the 12-year period, we identified mean differences (95% prediction interval) for BW: 2g (-48, 52); BWz: -0.04 (-0.16, 0.07); ΔW14: 40g (17, 62); ΔW14z: 0.16 (0.06, 0.25); W36: 129g (7, 189); W36z: 0.29 (0.16, 0.43). Evidence of reduced weight loss at day 14 and greater weight at 36w PMA was supported by estimates from unadjusted and adjusted regressions including adjustment for enteral nutritional intake. In babies who survived without major morbidity, weight gain following the period of early postnatal weight loss stabilised along parallel centile lines below birth centile in all gestational age groups. Differences in birth weight and early divergence in weight gain were apparent between babies that died or survived with major morbidity. Compared with babies without morbidities, the adjusted mean differences (95% CI) in W36z were lower in babies with severe brain injury -0.09 (-0.12, -0.07), treated retinopathy of prematurity -0.18 (-0.22, -0.14), and surgical necrotising enterocolitis -0.28 (-0.32, -0.23) but higher in babies with bronchopulmonary dysplasia 0.09 (0.07, 0.11).

Conclusions

The birth weight of babies born extremely and very preterm has remained stable over 12 years. Early postnatal weight loss has decreased, subsequent weight gain has increased; weight at 36W PMA is consistently below birth centile. Weight velocity in babies surviving without major morbidity appears to follow a consistent trajectory offering opportunity to construct longitudinal preterm growth curves despite lack of knowledge of optimal postnatal weight gain.

References *(include acknowledgement here if appropriate)*

1) Cole TJ, Statnikov Y, Santhakumaran S, Pan H, Modi N Birth weight and longitudinal growth in infants below 32 weeks gestation: a UK population study Arch Dis Child Fetal Neonatal Ed 2014; 99:F34-40
2) We acknowledge the contribution of all neonatal units comprising the UK Neonatal Collaborative

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: N Modi

Title (Upper case)

EARLY VERSUS DELAYED INITIATION OF PARENTERAL NUTRITION AFTER VERY PRETERM BIRTH

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

S Uthaya, N Longford, C Battersby, Kayleigh Ougham, Julia Lanoue, N Modi

Corresponding author e-mail address: s.uthaya@imperial.ac.uk

Institution(s)

Section of Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London. Chelsea and Westminster NHS Foundation Trust. London. UK

Introduction ***(include hypothesis)***

A current standard of care is to commence parenteral nutrition (PN) within hours of birth in all very preterm infants. However, trials in critically ill adults and children, including term infants have found short and long-term harms from early initiation of PN with effects on sepsis, duration of mechanical ventilation and hospital stay, renal replacement therapy, liver function, and health care costs. Of concern are reports of the long-term adverse impact on neurocognition and behaviour in children who received early PN with epigenetic changes in genes involved in brain development seen as early as three days after admission. We hypothesised that early initiation of PN would be associated with a lower rate of morbidity-free survival to discharge in very preterm infants.

Methods (*include source of funding and ethical approval if required)*

Design: Propensity matched analysis of population-level observational data held in the UK National Neonatal Research Database. **Setting:** National Health Service neonatal units in England and Wales **Participants:** Infants born below 31 weeks gestation between January 2008 and December 2019. **Exposures:** PN initiated in the first two days after birth (early); versus PN initiated after the second postnatal day (late). **Main outcomes**: The primary outcome was survival to discharge from neonatal care without major morbidities. Secondary outcomes were survival to discharge, growth and other core outcomes (late-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity and necrotising enterocolitis). The study was approved by the Health Research Authority, Health and Care Research Wales (IRAS project ID 273001).

Results

We included 65,033 infants in the analysis of whom 43,436 received early PN and 21,597 received late PN. With one-to-one matching there were 16,294 infants included in the matched cohort, 8147 in each treatment group. There was no evidence of a difference in survival to discharge without major morbidities (absolute rate difference (ARD) between early versus late 0.50%; 95% Confidence Interval (CI), -1.45, 0.45; p=0.29). Survival to discharge was higher in infants who received early PN (ARD -3.25%; 95% CI, -3.82 to -2.68; p<0.001) but they also had higher rates of late-onset sepsis (ARD -0.84%; 95% CI, -1.20 to -0.48; p<0.001), bronchopulmonary dysplasia (ARD -1.24%; 95% CI, -2.17 to -0.3; p=0.01), treatment for retinopathy of prematurity (ARD (-0.5%; 95% CI, -0.84 to -0.17; p<0.001), surgical procedures (ARD -0.8%; 95% CI, -1.40 to -0.20; p=0.01) and greater drop in weight z-score between birth and discharge (absolute difference 0.019; 95% CI, 0.003 to 0.039; p=0.02). We found no differences in the rates of severe necrotising enterocolitis (resulting in surgery or death), seizures or major brain injury.

Conclusions

The higher rate of survival but also of major morbidities in infants receiving early PN calls in to question current standard of care and justifies the need for a randomised controlled trial to determine the risks to benefits of early PN.

References ***(include acknowledgement here if appropriate)***

Verstraete S, et al. Lancet Respir Med. 2019;7(2):141-53. Verstraete S, et al. Crit Care. 2018;22(1):38. Guiza F, et al. Lancet Respir Med. 2020;8(3):288-303.

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: X☐

Senior author supporting presentation on day of meeting: N/A

Title (Upper case)

INVOLVING PARENTS, PATIENTS AND CLINICIANS IN THE DESIGN OF A UK NATIONAL DOUBLE-CLUSTER PRAGMATIC RANDOMISED CONTROLLED TRIAL

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

William Lammons, Becky Moss, Cheryl Battersby, Daphne Babalis, Victoria R Cornelius, Neena Modi

Corresponding author e-mail address: w.lammons@imperial.ac.uk

Institution(s)

1) Section of Neonatal Medicine, School of Public Health, Faculty of Medicine, Imperial College London; Chelsea and Westminster NHS Foundation Trust; 2) Imperial Clinical Trials Unit, Imperial College London

Introduction *(include hypothesis)*

We are developing a double-cluster, national randomised controlled trial (COLLABORATE) to resolve two longstanding comparative effectiveness uncertainties in the nutritional care of very preterm babies; the benefits of i) pasteurised human donor milk vs preterm formula to supplement insufficient own mother's milk volume; ii) routine versus no routine protein-carbohydrate fortification of human milk. We sought parent, patient, and clinician perspectives on trial rationale, design, acceptability, and recruitment.

Methods (*include source of funding and ethics approval if required)*

We invited voluntary participation through a national webinar, the neoWONDER group, and NEC UK. We conducted focus groups and semi-structured interviews to gauge the trial's acceptability with parents and adults born preterm, and separately with neonatologists, a midwife and a dietician. We created a topic guide to elicit views on cluster randomisation (by unit rather than individual level), trial information leaflet (explaining this is comparative effectiveness study) and opt-out consent process (inclusion is the default). We used qualitative coding and thematic analysis of the data to analyse results. We followed the COREQ checklist (Tong el al 2007).

Results

Our analysis identified 4 themes among patients and parents: pressure on mothers to breastfeed; opt-out consent as reducing stress; the need for research to be a partnership between clinicians, parents, and researchers; and the need for information to be presented in a collaborative tone, allowing parents to assimilate information at their own pace. Clinicians also felt the opt-out consent procedure could reduce parental burden, but felt anxious this might hinder parents' recall of consenting. Some clinicians felt constrained by their own beliefs and the conflicting opinions in clinical teams. Some expressed difficulty in either accepting the evidence of uncertainty regarding optimum feeding methods or in accepting the evidence of uncertainty as justification for a trial. We also identified misunderstandings of the central principles of randomised controlled trials.

Conclusions

By involving parent, patients and clinicians we found ways to mitigate anxieties for all groups centred upon developing a strong partnership approach. Specific design elements were confirmation of use of opt-out consent, a 2-sided information sheet to allow parents access information at their own pace, and use of language that parents perceive as inclusive and participatory. There is need to develop ways to assist clinicians in acknowledging and communicating uncertainty.

References *(include acknowledgement here if appropriate)*

Tong A, Sainsbury P, Craig J Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care* 2007; *19*:349-57

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Professor Neena Modi

Title (Upper case)

The INTERGROWTH-21st Project International INTER-NDA standards for child development at two years of age: An International Prospective Population-based Study

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Michelle Fernandes[1,2] (introduced by Dr Richard Thwaites), José Villar[2], Alan Stein[3], Eleonora Staines Urias[2], Fernando C. Barros[4], Enrico Bertino[5], Manorama Purwar[6], Maria Carvalho[7], and Stephen H. Kennedy[2].

Corresponding author e-mail address: m.c.fernandes@soton.ac.uk

Institution(s)

[1]Department of Paediatrics, University of Southampton, UK [2]Nuffield Department of Women's & Reproductive Health, University of Oxford, UK [3]Department of Psychiatry, University of Oxford, UK [4]Universidade Católica de Pelotas, Brazil [5]Universita di Torino, Italy [6]Ketkar Hospital, Nagpur, India [7]Aga Khan University, Nairobi, Kenya

Introduction ***(include hypothesis)***

An estimated 250 million children, worldwide, are at risk of sub-optimal development by 5 years of age. While international WHO standards exist for child growth, no such standards exist for child development. This project aimed to construct international standards for child development, from cognitive, language, motor and behaviour outcomes measured in optimally healthy and nourished 2-year olds in the INTERGROWTH-21st Project.

Methods (*include source of funding and ethical approval if required)*

In this population-based cohort study, comprehensive health, growth and neurodevelopmental data were prospectively collected, from early pregnancy to 2 years post-birth, in 1181 children from Brazil, India, Italy, Kenya and the UK. These children were prospectively recruited from early fetal life according to the prescriptive WHO approach, and confirmed to be at low risk of adverse perinatal and postnatal outcomes. Child development was measured on the INTER-NDA. Vision (Cardiff tests), attentional problems (CBCL), and growth (WHO protocols) were also measured. Funding: Bill & Melinda Gates Foundation. Ethics approval from all sites.

Results

Scaled INTER-NDA domain scores are presented as centiles, which were constructed according to the prescriptive WHO approach and excluded children born preterm and those with significant postnatal/neurological morbidity. For all domains, except negative behavior, higher scores reflect better outcomes and the threshold for normality was defined as ≥ 10th centile. For the INTER-NDA's cognitive, fine motor, gross motor, language and positive behaviour domains these are ≥38.5, ≥25.7, ≥51.7, ≥17.8, and ≥51.4, respectively. The threshold for normality for the INTER-NDA's negative behaviour domain is ≤50.0, i.e. ≤90th centile. At 22 to 30 months of age, the cohort overlapped with the WHO motor milestone centiles, showed low postnatal morbidity (<10%), and vision outcomes, attentional problems and emotional reactivity scores within the respective normative ranges.

Conclusions

From this healthy and well-nourished, international cohort, we have constructed, using the WHO prescriptive methodology, international INTER-NDA standards for child development at 2 years of age. Standards, rather than references, are recommended for population-level screening and the identification of children at risk.

References ***(include acknowledgement here if appropriate)***

Fernandes M, et al, the BMJ (in press, 2020); Villar J, et al, Nature Communications 2019; Fernandes M, et al, PLoS ONE 2014; Murray E et al, PLoS ONE 2018. Acknowledgements: Study participants, site teams.

Check box if presenting author is a trainee: basic science trainee ☐ clinical trainee ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: -

Title (Upper case)

INDIVIDUAL DIFFERENCES IN BRAIN DEVELOPMENT AND COGNITIVE OUTCOME IN INFANTS WITH CONGENITAL HEART DISEASE

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Alexandra F Bonthrone[1], Ralica Dimitrova[1,2], Andrew Chew[1], Christopher J Kelly[1], Lucilio Cordero-Grande[1,5], Olivia Carney[1], Alexia Egloff[1], Emer Hughes[1], Katy Vecchiato[1,2], John Simpson[3], Joseph V Hajnal[1], Kuberan Pushparajah[3], Suresh Victor[1], Chiara Nosarti[1,4], Mary A Rutherford[1], A David Edwards[1], Jonathan O'Muircheartaigh[1,2], Serena J Counsell[1]

Corresponding author e-mail address: serena.counsell@kcl.ac.uk

Institution(s)

1. Centre for the Developing Brain, School of Biomedical Engineering and Imaging Sciences, King's College London; 2. Department for Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London; 3. Paediatric Cardiology Department, Evelina London Children's Healthcare; 4. Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London; 5. Biomedical Image Technologies, ETSI Telecomunicación, Universidad Politécnica de Madrid and CIBER-BBN

Introduction *(include hypothesis)*

Infants with Congenital Heart Disease (CHD) are at risk of neurodevelopmental impairments (1), the origins of which are currently unclear. We hypothesised that impaired neonatal volumetric brain development is associated with reduced cerebral oxygen delivery and lower neurodevelopmental scores at 22 months in this population.

Methods (*include source of funding and ethical approval if required)*

Sixty-six infants [39 male, median (range) gestational age at birth = 38.50 (34.86-41.57) weeks; postmenstrual age at scan median (range) = 39.29 (37.43-42.29) weeks] underwent brain MRI prior to surgery on a 3T MRI scanner situated on the neonatal unit at St Thomas' Hospital, London. T2-weighted images were segmented into brain regions using a neonatal-specific algorithm (2). We generated normative curves of typical volumetric brain development using a data-driven technique applied to 219 healthy infants from the Developing Human Connectome Project (dHCP) (3). Atypicality indices, representing the degree of positive or negative deviation of a regional volume from the normative mean for a given gestational age, sex and postnatal age, were calculated for each infant with CHD. Extreme deviations from typical brain development were taken as atypicality indices >±2.6. Cerebral oxygen delivery (CDO_2) was calculated from phase contrast angiography in 53 infants with CHD. Cognitive and motor abilities were assessed at 22 months (N=46) using the Bayley-III. We assessed the relationship between atypicality indices, CDO_2 and cognitive and motor outcome. We also examined whether CDO_2 was associated with neurodevelopmental outcome through the mediating effect of regional brain volumes.

The National Research Ethics Service West London committee provided ethical approval (CHD: 07/H0707/105; dHCP: 14/LO/1169). This research was funded by the Medical Research Council UK, the British Heart Foundation, and Action Medical Research. The Developing Human Connectome Project was funded by the European Research Council. This research was supported by the Wellcome EPSRC Centre for Medical Engineering at Kings College London and by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and Kings College London.

Results

Extreme deviations in development were identified in extracerebral CSF, ventricles and subcortical brain structures. Negative atypicality indices in bilateral caudate, thalami and the left lentiform nucleus were associated with both reduced neonatal CDO_2 (p_{FDR}<0.047) and poorer cognitive abilities at 22 months (p_{FDR}=0.04). There was a significant indirect relationship between CDO_2 and cognition through the mediating effect of negative caudate and thalami atypicality indices (p_{FDR}<0.027).

Conclusions

Lower cognitive abilities in toddlers with Congenital Heart Disease were associated with smaller deep grey matter volumes prior to cardiac surgery. The aetiology of poor cognition may encompass reduced cerebral oxygen delivery leading to impaired grey matter growth. Interventions to improve cerebral oxygen delivery may promote early brain growth and improve cognitive outcomes in infants with Congenital Heart Disease.

References *(include acknowledgement here if appropriate)*

(1) Marino, B.S. et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation (2012). 126.
(2) Makropoulos, A. et al. Automatic whole brain MRI segmentation of the developing neonatal brain. IEEE Trans Med Imaging (2014). 33
(3) Dimitrova, R. et al. Individualized characterization of volumetric development in the preterm brain. bioRxiv 2020: 2020.08.05.228700.

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Prof Serena Counsell

Title (Upper case)

MELATONIN ALTERS SYSTEMIC CYTOKINE PRODUCTION IN NEONATAL ENCEPHALOPATHY

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Tim Hurley[1], Lynne Kelly[1], Aoife Branagan[2], Eleanor J Molloy[1,2,3]

Corresponding author e-mail address:	tim.hurley@ucdconnect.ie

Institution(s)

1. Department of Paediatrics and Child Health, Trinity College Dublin, Ireland
2. Department of Neonatology, Coombe Women and Infant's University Hospital, Dublin, Ireland
3. Department of Neonatology, Children's Health Ireland at Crumlin and Tallaght, Dublin, Ireland

Introduction *(include hypothesis)*

Despite routine use of therapeutic hypothermia (TH) for neonatal encephalopathy (NE) a significant group have associated mortality or severe disability. Adverse outcome in NE is associated with dysregulated inflammation which may be targeted for neuroprotection. Melatonin is a potent anti-inflammatory, anti-oxidant and anti-apoptotic agent and is a safe and effective therapy in animal models of NE with promise in early human trials. The objective was to examine the ex-vivo effects of melatonin treatment on inflammatory responses in NE.

Methods (*include source of funding and ethical approval if required)*

Infants diagnosed with moderate-severe NE, who were undergoing TH, were prospectively recruited (n=36) and compared to neonatal controls (n=18). Serial serum samples were collected during the first week of life and treated with melatonin, lipopolysaccharide (LPS) or both and cytokine production measured with multi-plex ELISA for EPO, GMCSF, IFNγ, IL1α, IL1RA, IL1β, IL2, IL6, IL8, IL10, IL18, TNFα, TNFβ, and VEGF. Ethical approval was granted from each clinical site, and written informed consent was required prior to recruitment to the study.

Results

In NE, melatonin significantly reduced GMCSF and IFNγ and increased IL1RA, IL8, TNFα, and VEGF. Infants with NE had significantly lower IFNγ, IL10, IL18, and VEGF than controls in response to melatonin. In NE LPS stimulated samples, melatonin significant increased EPO, GMCSF, IFNγ, IL1RA, IL2, IL6, IL8, IL10, IL18, TNFα, TNFβ, and VEGF and further increased in controls for the following: EPO, IL1RA, IL6, IL8, TNFα with significantly lower IL2.

Conclusions

Infants with NE had significantly reduced cytokine responses compared with controls in response to melatonin as well as LPS. Melatonin is a potent immunomodulator in NE undergoing TH and may have therapeutic potential.

References *(include acknowledgement here if appropriate)*

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☒

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Professor Eleanor Molloy

Title (Upper case)

APOPTOTIC NEURONAL CELL DEATH IN NEONATAL ENCEPHALOPATHY IS REGULATED BY THE HIPPO-YAP-LET-7B AXIS

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Ponnusamy V[1,2], Ip R[2], Clarke P[3,4], Wozniak E[2], Mein C[2], Schwendimann L[5], Barlas A[6], Chisholm P[7], Chakkarapani E[8], Michael-Titus AT[2], Gressens P[5], Yip PK[2] & Shah DK[2,6]

Corresponding author e-mail address: vennilaponnusamy@nhs.net

Institution(s)

[1]Ashford and St. Peter's Hospitals, Chertsey; [2]Queen Mary University of London; [3]Norfolk and Norwich University Hospitals; [4]University of East Anglia; [5]Université de Paris, NeuroDiderot, Inserm, Paris; [6]The Royal London Hospital; [7]Homerton University Hospital; [8]Translational Health Sciences, University of Bristol.

Introduction *(include hypothesis)*

With increasing knowledge on microRNAs (miRNAs) as biomarkers of various adult and paediatric conditions, we hypothesised that candidate miRNAs would be linked to the neuronal cell death or neuro-inflammatory pathways involved in the pathogenesis of neonatal encephalopathy (NE). We aimed to identify and study the role of a candidate miRNA as a biomarker of brain injury in neonates with moderate to severe NE using dried blood spots (DBS).

Methods (*include source of funding and ethical approval if required)*

With ethical approval and consent, DBS from neonates with NE were processed using unbiased miRNA next generation sequencing and further validated with RT-qPCR. Hierarchical clustering and KEGG pathway analysis were used to identify a candidate miRNA associated with the apoptotic Hippo pathway. Mechanistic studies were performed on glucose deprived cell cultures and two animal models of perinatal brain injury: hypoxic-ischaemic and intrauterine inflammation models using fluorescent in-situ hybridisation and immunohistochemistry.

Results

Let-7b-5p was noted to be a significant miRNA with increased peripheral expression in DBS of the newborns with moderate to severe NE with adverse outcomes when compared to those with mild NE. Apoptotic neuronal cell death was noted with an overall significant increase in neuronal cleaved caspase-3 expression ($p < 0.01$) in the cerebral cortex of both animal models. In comparison to the controls, the percentage of neuronal let-7b-5p expression (mean +/- SEM) in the cerebral cortex was reduced in both ipsilateral (69.9 +/- 2.3, $p < 0.001$) and contralateral (74.0 +/- 2.8, $p < 0.001$) sides in the hypoxic-ischaemic model and the intrauterine inflammation model (71.4 +/- 5.8, $p < 0.001$). Similar results were noted in glucose deprived cultures compared to controls (50.78 +/- 1.36 vs 11.23 +/- 1.10 % area, $p < 0.001$). The changes in let-7b-5p expression corresponded with activated Hippo pathway, with a significant increase ($p < 0.001$) in neuronal/nuclear ratio of Yes Associated Protein (YAP) in both in vitro and in vivo studies.

Conclusions

Reduced nuclear YAP with decreased intracellular let-7b-5p correlated with neuronal apoptosis in conditions of metabolic stress, as observed in NE. This novel finding of the Hippo-YAP-let-7b axis needs validation in larger cohorts and other models of NE to further our knowledge on let-7b-5p as a biomarker for NE.

References *(include acknowledgement here if appropriate)*

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Dr Divyen Shah

Title (Upper case)

REGULATION OF NEUROINFLAMMATION AND GLUTAMATE TRANSPORT IN A TERM NEWBORN RAT MODEL OF HYPOXIC-ISCHEMIC BRAIN INJURY

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Pregnolato S[1], Luyt K[1], Sabir H[2], Isles AR[3], Chakkarapani E[1]

Corresponding author e-mail address:	sp16027@bristol.ac.uk

Institution(s)

1. University of Bristol, Neonatal Neurology
2. University of Bonn, Neonatology and Pediatric Intensive Care
3. Cardiff University, Psychological Medicine and Clinical Neurosciences

Introduction *(include hypothesis)*

In the term brain, moderate-severe hypoxia-ischemia induces inflammation and glutamate excitotoxicity, possibly via dysregulation of candidate pro-inflammatory cytokines (e.g. *Tnfα*, *Il1β*, *Il6*) and candidate astrocytic glutamate transporter (*Glt1*). Epigenetic mechanisms may mediate such dysregulation. Hypotheses: 1) hypoxia-ischemia dysregulates mRNA expression of these candidate genes; 2) expression changes are mediated by DNA methylation changes; 3) methylation values in brain and blood are correlated; 4) including imprinted gene *Peg3* improves robustness of DNA methylation methodology.

Methods (*include source of funding and ethical approval if required)*

7-days-old rat pups (n=42) were assigned to 9 groups based on treatment (for each timepoint: naïve (n=3), sham (n=3), hypoxia-ischemia (n=8)) and timepoint for tissue collection (6h, 12h, 24h post-hypoxia). Moderate hypoxic-ischemic brain injury was induced via ligation of the left common carotid artery followed by 100 min hypoxia (8% O_2, 36°C). mRNA was quantified in cortex and hippocampus for the candidate genes, alongside myelin (*Mbp*), astrocytic (*Gfap*) and neuronal (*Map2*) markers (qPCR). DNA methylation was measured for *Glt1* in cortex and blood (bisulfite pyrosequencing).

Results

Hypoxia-ischemia induced pro-inflammatory cytokine expression in both brain regions ($p \leq 0.05$ at all timepoints, trend for 6h peak), accompanied by astrogliosis and myelin injury.

There was no significant evidence of *Glt1* suppression or methylation changes. Evidence strengthened slightly after merging naïve and sham, suggesting re-assessment after isolating astrocytes.

Robust *Peg3* data confirms accurate methylation quantification.

Conclusions

This small study supports the important role of neuroinflammation caused by acute hypoxia-ischemia in the term brain and prioritises methylation analyses focusing on this pathway. Relevant epigenetic blood biomarkers may facilitate identification of high-risk newborns at birth, maximising chances of treatment.

References *(include acknowledgement here if appropriate)*

1. Pregnolato et al (2019) *Front Physiol* 10: 417 2. Fleiss and Gressens (2012) *Lancet Neurol* 11 (6): 556
The protocol was approved by the animal welfare and ethics board, University of Bristol. All animal experiments were performed in accordance to the ARRIVE guidelines with government approval by the State Agency of Nature, Environment and Consumer Protection North Rhine-Westphalia, Germany.

Check box if presenting author is a trainee: basic science trainee ☒ clinical trainee ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Prof Karen Luyt

Title (Upper case)

Assessment of the repeatability and reliability of ultrasound measurement of the new-born corpus callosum and comparison with MRI

S Williams[1], D Buckley[3], M Mills[4] R Fernandez[1], M Suttie[2], R Huang[2], JA Noble[2], N Aiton[1,3]

Corresponding author e-mail: Sam.williams6@nhs.net; neil.aiton@nhs.net

Institution(s)

1) Brighton & Sussex Medical School, Brighton, UK, 2) University of Oxford, UK 3) Brighton & Sussex University Hospitals NHS Trust, 4) St George's University Hospital Foundation Trust.

Introduction *(include hypothesis)*

The corpus callosum is an important white matter tract allowing neural transmission between different areas of the brain. Development occurs early in fetal life between weeks 10-21. Changes have been observed in the shape of the corpus callosum in response to prenatal alcohol exposure using MRI in children and adults. Ultrasound can be used to image the corpus callosum in the neonatal period, and we hypothesise that ultrasound can be used to detect these differences. It is therefore necessary to examine the repeatability and reliability of corpus callosum measurements of ultrasound when compared with MRI.

Methods (*include source of funding and ethical approval if required)*

A retrospective cohort study of 40 term infants with mild/moderate hypoxic-ischaemic encephalopathy, MRI and ultrasound imaging in a UK tertiary neonatal centre. Scans were extracted and anonymised, so ethical approval not required. A manual segmentation programme was developed using Matlab (Mathworks). The corpus callosum was outlined in the midline sagittal plane to derive measurements of area, perimeter, and length. Intra-rater repeatability and inter-rater repeatability, intra-class correlation coefficients, 95% confidence intervals and Bland-Altman plots used to measure correlation and agreement. Comparison was also made using digital surface modelling techniques with principle component analysis, to enable complexity of shape to be incorporated into later models.

Results

Moderate to good correlation was found between MRI and ultrasound for surface area (ICC 0.73; 95% CI 0.53 – 0.85). Poor to good correlation for perimeter (ICC 0.63; 95% CI 0.40 – 0.79) and poor to moderate correlation for length (ICC 0.53, 95% CI 0.25 – 0.72) was also seen. This study also found moderate to good intra-rater correlation for ultrasound surface area (ICC 0.83; 95% CI 0.73 – 0.90), and good to excellent intra-rater correlation for both perimeter (ICC 0.90; 95% CI 0.84 – 0.94) and length (ICC 0.93; 95% CI 0.89 – 0.96). Inter-rater ultrasound reliability was significantly lower, with poor to moderate correlation for surface area (ICC 0.29; 95% CI 0.02 – 0.61), and poor correlation for perimeter (ICC -0.05; 95% CI -0.27 – 0.31) and length (ICC -0.01; 95% CI -0.22 – 0.34), however significant confounding factors were identified.

Conclusions

This study demonstrates the level of correlation and agreement between ultrasound and MRI for the measurement of the newborn corpus callosum. This will allow the greater confidence in interpretation of results between the two modalities. Further work is need to optimise and standardise the methodology of ultrasound scan acquisition to make further improvements reliability. This work will allow the comparison between infants with and without prenatal alcohol exposure.

References *(include acknowledgement here if appropriate)*

(1) Clarke ME, Gibbard WB. Overview of fetal alcohol spectrum disorders for mental health professionals. Can Child Adolesc Psychiatr Rev. 2003;12(3):57-63 (2) NHS. Foetal alcohol syndrome 2020 [Available from: https://www.nhs.uk/conditions/foetal-alcohol-syndrome/ (3) Inform N. Alcohol and Pregnancy 2020 [Available from: https://www.nhsinform.scot/ready-steady-baby/pregnancy/looking-after-yourself-and-your-baby/alcohol-and-pregnancy (4) CDC. Fetal Alcohol Spectrum Disorders (FASDs) 2020 [Available from: https://www.cdc.gov/ncbddd/fasd/facts.html
(5) Nosarti C, Rushe T, Woodruff P, Stewart A, Rifkin, L., Murray R. Corpus callosum size and very preterm birth: relationship to neuropsychological outcome (6) (SIGN) SIGN. Children and young people exposed prenatally to alcohol. Edinburgh: SIGN (SIGN publication no. 156); 2019

Acknowledgements: Dr Muzaffar Malik from Brighton & Sussex Medical School, Dr Dannika Buckley, and Michael Mills

Check box if presenting author is a trainee: Sam Williams is a clinical trainee

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented

Senior author supporting presentation on day of meeting: Dr Neil Aiton

Title (Upper case)

ASSOCIATION BETWEEN PRETERM BIRTH, DIFFERENTIAL DNA METHYLATION AND BRAIN DYSMATURATION

Authors *(Presenting author underlined)*

Emily N. W. Wheater[1], Paola Galdi[1], Daniel McCartney[2], Manuel Blesa[1], Gemma Sullivan[1], David Q. Stoye[1], Gillian J. Lamb[1], Sarah Sparrow[1], Mark E. Bastin[3,4,7], Lee Murphy[6], Riccardo Marioni[2,4], Simon R. Cox[4,5,7], James P. Boardman[1,3]

Corresponding author e-mail address: James.Boardman@ed.ac.uk

Institution(s)

1) MRC Centre for Reproductive Health; 2) Centre for Genomic and Experimental Medicine; 3) Centre for Clinical Brain Sciences; 4) Lothian Birth Cohorts; 5) Department of Psychology, 6) Edinburgh Clinical Research Facility, Western General Hospital, UK; 7) Scottish Imaging Network, A Platform for Scientific Excellent (SINAPSE) Collaboration. All University of Edinburgh, United Kingdom.

Introduction *(include hypothesis)*

Preterm birth is closely associated with a phenotype consisting of brain network dysconnectivity inferred from neonatal diffusion MRI (dMRI) neurocognitive impairment in childhood. DNA methylation (DNAm) is highly dynamic through fetal brain development with a global reduction in methylation being associated with increasing gene expression through development (1). Preterm birth is associated with profound changes in DNAm in umbilical cord blood (2) but changes in DNAm in saliva, a more accessible tissue for neonatal studies, is less well characterised. We tested the hypotheses that 1) gestational age (GA) at birth is associated with generalised differential DNAm in saliva, and 2) there is a relationship between GA at birth, differential DNAm, and dMRI markers of brain network dysconnectivity.

Methods (*include source of funding and ethical approval if required)*

Participants were preterm and term neonates, and recruited to a longitudinal study to investigate the effect of preterm birth on brain development (3). Saliva and brain MRI were acquired at term equivalent age. The Illumina EPIC array was used for an epigenome wide assessment of differential DNAM in association with GA, and functional analysis was performed to identify gene sets that were enriched on the basis of probes that contributed either to differentially methylated probes (DMPs) or regions (DMRs). Following dimension reduction of DMPs that reached genome-wide significance using principal component analysis, we investigated associations between DNAm and peak width skeletonized dMRI mean diffusivity (PSMD), fractional anisotropy (PSFA) and neurite dispersion index (PSNDI) (4). Ethical approval was granted by NRES (11/55/0061 and 13/SS/0143).

Results

Participants were 258 infants with GA range 23-42 weeks. Mean age at saliva sample collection and MRI was 41.2 weeks (range: 37.7–47.1 weeks). GA at birth is associated with extensive differential methylation across the genome, with 8898 DMPs reaching genome wide significance ($p<3.6x10^{-8}$), and 1775 DMRs in analyses adjusted for birthweight z-score, infant sex, gestational age at sampling, maternal smoking, estimated epithelial cell proportion and surrogate variables. Functional analysis identified 14 enriched gene ontology terms pertaining to cell-cell contacts, and cell-extracellular matrix contacts. The first principal component (PC1) accounted for 23.5% of variance and was negatively associated with GA at birth ($r=-0.622$; $p<2.2x10^{-16}$). PSMD and PSNDI were also associated with GA at birth (PSMD: $\beta=-0.645$, $p<2x10^{-16}$; PSNDI: $\beta=-0.388$, $p=1.08x10^{-5}$). PC1 was significantly associated with PSMD ($\beta=0.344$, $p=2.55x10^{-7}$) and PSNDI ($\beta=0.360$, $p=5.07x10^{-5}$), but not with PSFA ($\beta=-0.017$, $p=0.802$).

Conclusions

Gestational age at birth has a profound impact on the neonatal saliva methylome at term equivalent age, with differential DNAm being observed across the genome. Associations between GA at birth and both DNAm and image markers of dysconnectivity, and between DNAm and image features, suggest that differential DNAm contributes, in part, to the relationship between GA and brain network dysconnectivity in preterm infants. Salivary samples offer an accessible tissue for studying the methylome in neonates.

References *(include acknowledgement here if appropriate)*

1) H. Spiers, et al., Genome Res., (2015); 2) S.K. Merid, et al., Genome Med. (2020); 3) J.P. Boardman, et al., BMJ Open, (2020). 4) M. Blesa, et al., Front. Neurol. 2020. ENWW is supported by the Wellcome Trust Translational Neuroscience PhD fellowship programme at the University of Edinburgh (203769/Z/16/A). This work was supported by Theirworld (www.theirworld.org) and was undertaken in the MRC Centre for Reproductive Health,

basic science trainee x☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: x☐

Senior author supporting presentation on day of meeting: James P. Boardman

Title (Upper case)

NEONATAL HEALTH CARE COST OF PRETERM BABIES BORN BETWEEN 27-31 WEEKS IN ENGLAND: RETROSPECTIVE ANALYSIS OF A NATIONAL BIRTH COHORT USING THE OPTI-PREM DATASET

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

Miaoqing Yang, Tilly Pillay, Elaine Boyle, Neena Modi, Oliver Rivero-Arias

Corresponding author e-mail address:	Oliver Rivero Arias: oliver.rivero@npeu.ox.ac.uk

Institution(s)

[1] National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford
[2] University of Leicester NHS Trust, University of Wolverhampton
[3] Department of Health Sciences, University of Leicester
[4] Section of Neonatal Medicine, School of Public Health, Chelsea and Westminster campus, Imperial College London

Introduction *(include hypothesis)*

Annual NHS health expenditure to care for preterm babies born between 27 and 31 weeks gestation (27-31 GWK) is substantial. UK published cost figures for this group vary widely and are almost a decade old, which may no longer reflect current standard of practice. In this study, we aim to estimate neonatal health care costs up to hospital discharge of babies born between 27-31 GWK in Local Neonatal Units (LNU) and Neonatal Intensive Care Units (NICU) in England, from 2014 to 2018. The cost study is part of the OPTI-Prem study[1] to assess the best place of care for babies born between 27-31 GWK in England.

Methods (*include source of funding and ethical approval if required)*

We conducted an analysis of the OPTI-Prem national birth cohort derived from the National Neonatal Research Database (NNRD). Detailed cost analysis was performed from the NHS perspective covering different levels of neonatal care estimated using unit costs from reference costs (2018/2019 prices). We also calculated the cost of major specialised clinical activities not included in the reference costs using unit costs from the literature, finance departments and expert opinion. Descriptive statistics and regression analyses were used to estimate the relationship between gestational age at birth and economic costs. This study is funded by the National Institute for Health Research, Health Services and Delivery Research Stream, Project number 15/70/104. We have obtained research ethics approval (IRAS Reference No 212034).

Results

The mean (SD, median) length of stay of initial hospitalisation for a preterm baby born 27-31 GWK in a neonatal unit in England is 50.9 (25.4, 46.0) days. The average cost (SD) was estimated to be £46,605 (£30,168), varying from £79,339 (£36,986) per infant born at 27 GWK to £28,544 (£16,016) per infant born at 31 GWK. Across all gestational ages, 28% of total costs were associated to intensive care, 26% to high-dependency care, 45% to special care and 1% to hospital transfers. The proportion of total costs associated to intensive care was significantly higher for babies of lower gestational age, reaching almost 36% at 27 GWK and 33% at 28 GWK.

Conclusions

The findings of this study support an increasing evidence base that suggest an inverse relationship between neonatal costs and gestational weeks at birth. The economic costs reported here exceed the costs of moderately and late preterm infants, but are smaller than that of extremely preterm infants. As a next step, we will compare the cost-effectiveness outcomes of babies who were treated in either type of unit and assess the best place of care for such babies to support the development of national policies.

References *(include acknowledgement here if appropriate)*

1. OPTI-Prem study website: https://clinicaltrials.gov/ct2/show/NCT02994849.

Check box if presenting author is a trainee: **basic science trainee** ☐ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting:

Title (Upper case)

EARLY LIFE OXYGEN DYSREGULATION AND GRAM-POSITIVE BACTERIAL CHALLENGE IN A NEONATAL RAT MODEL INDUCES AN INFLAMMATORY RESPONSE BUT VENTILATORY CONTROL IS MAINTAINED DURING NORMOXIA.

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society) James Boardman*

Maria D. Casacão[1,2], Karen M. O'Connor[1,2], Dempsey EM[2,3], Ken D. O'Halloran[1,2], Fiona B. McDonald[1,2]

Corresponding author e-mail address: fiona.mcdonald@ucc.ie

Institution(s)

1. Department of Physiology, School of Medicine, College of Medicine and Health, University College Cork, Cork, Ireland.
2. Irish Centre for Maternal and Child Health Research, University College Cork, Cork, Ireland.

Introduction *(include hypothesis)*

Very preterm infants, are at an increased risk of early life infection as a result of their immaturity and prolonged hospital stays. Preterm immaturity is characterised by unstable respiratory control with male infants exhibiting particular vulnerability. Oxygen fluctuations during early life have been previously demonstrated to cause persistent alterations in the control of breathing. Late onset infection is a major challenge in very preterm infants. Proteins from Gram-positive bacteria such as LTA (Lipoteichoic Acid) and PGN (Peptidoglycan) are known to mediate systemic inflammation through Toll-like receptors. We hypothesised that chronic exposure to intermittent hypoxia and hyperoxia (cIHH) prior to a subsequent Gram-positive bacterial infection would cause cardiorespiratory dysregulation.

Methods (*include source of funding and ethical approval if required)*

This study was conducted in line with European regulations and approved by local animal ethics committee at University College Cork and the national regulatory body, HPRA, Ireland. Sprague Dawley rat litters (male and female pups) were exposed for 10 consecutive days to either SHAM or cIHH treatment from postnatal day (PND) 3 to PND12. On PND13 the pups were studied using whole body plethysmography. Baseline measurements of breathing and rectal temperature were assessed and the animals were then monitored for 3 hours under normoxic conditions following intraperitoneal (i.p.) administration of LTA+PGN or vehicle (saline) solution (n=10/group). CO_2 production was measured throughout the experiment and rectal temperature was taken at the end of the experiment. In a separate cohort of animals which underwent the same intervention, respiratory muscle function (1,3 and 5 hours post i.p.), plasma cytokine concentrations (27-Plex Multiplex array- 3 hours post i.p.) and plasma corticosterone concentration (ELISA- 1 hour post i.p.) was assessed in both males and female rats. All data were analysed using a 3-way ANOVA (factors: sex, gas, drug).

Results

Our results reveal that administration of LTA+PGN increased plasma concentrations of MIP-1α, GRO/KC, MIP-2, IP-10, IL1a, IL-5, IL-10, fracktalkine and MCP-1; sex was not a significant factor despite evidence of sex-differences in toll-like receptors. LTA&PGN administration stimulated an increase in leptin cytokine/hormone that was potentiated by prior cIHH exposure. Corticosterone was equivalent across groups. We observed a decrease in breathing frequency in both SHAM/cIHH groups treated with LTA&PGN that corresponded with a decrease in metabolism (drug $p \leq 0.05$) such that the ventilatory equivalent (ventilation normalised to metabolism) was unchanged. There was no evidence that respiratory muscle function was compromised.

Conclusions

Further investigation is warranted to understand how oxygen dysregulation influences leptin production and if this influences respiratory behaviour in response to stress (e.g. responses to hypoxia). This will contribute to our understanding of both the vulnerability and resilience of preterm babies.

References ***(include acknowledgement here if appropriate)***

The project was funded by Science Foundation Ireland; University College Cork, School of Medicine, Translational Research Access Programme and the Department of Physiology, University College Cork,

Check box if presenting author is a trainee: **basic science trainee** ☒ **clinical trainee** ☐

All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Fiona McDonald

Title (Upper case)

Using 3D photography and imaging analysis to detect prenatal alcohol exposure

Authors *(Presenting author underlined. If no author is a Society member please provide the name of the member introducing the author to the Society)*

N Aiton[1], A Ferguson[1], J Smith[1], M Suttie2

Corresponding author e-mail address:	neil.aiton@nhs.net

Institution(s)

1)One Stop Clinic (pregnancy and substance misuse), Brighton and Sussex University Hospitals NHS Trust
2)Nuffield Dept. Women's & Reproductive Health, Big Data Institute, University of Oxford. UK

Introduction ***(include hypothesis)***

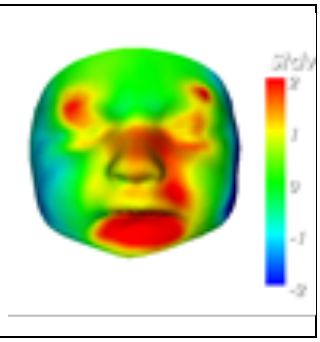
The knowledge that prenatal alcohol exposure affects facial development was first published over 40 years ago. The three specific features are relatively unique to alcohol exposure: small palpebral fissures, smooth philtrum and thin top lip, and can be used as part of the diagnostic process.
Does the use of 3D photography add additional diagnostic utility when compared with standard assessment?

Methods (*include source of funding and ethical approval if required)*

Non-randomised anonymised observational cohort study: HRA approval obtained. recruited from the postnatal ward of teaching hospital on South Coast of UK. Mothers completed a lifestyle questionnaire including information on alcohol consumption in pregnancy. Three pictures were taken of the newborn infants using a 3D camera (Canfield H1 and reconstituted to a 3D image. These were processed and analysed using 3D digital surface modelling techniques with principal component analysis.The images were decolourised and geometric surface topology extracted. They normalised to a standard size so that comparisons could be made.

Results

Total recruitment n=761 (379 mothers and 382 babies). Results were analysed according to the level of reported alcohol exposure. 5% women did not realise they were pregnant until after 8 weeks. 3.5% continued to drink >4 units per week occasionally or regularly during pregnancy. The facial images of Infants who were not exposed to alcohol in pregnancy could be built into a multi-component model to represent the normal values for surface shape characteristics. Alcohol-exposed infants could be compared with this model using coloured images to represent the statistical variation from the normal values. Pure red and blue colours represents +/- 2 SD lower or higher than normal values respectively.



Conclusions

It is possible to use this method to distinguish infants with significant prenatal alcohol exposure. It is also possible to detect and measure additional features which do not form part of the current standardised assessment. Further work will determine the utility and practicality of this type of imaging in diagnosis of FASD.

References ***(include acknowledgement here if appropriate)***

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Ref: Jones K, Smith D. Recognition of the fetal alcohol syndrome. Lancet 1973, Vol 302: 999-1001

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All authors have approved the abstract, actual or potential conflicts of interest have been declared to the meetings secretary, and the abstract has not been presented previously: ☒

Senior author supporting presentation on day of meeting: Neil Aiton