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Neonatal outcomes following early fetal growth restriction: a subgroup analysis of the EVERREST Study

Lingam I[1,2], Okell J[1], Maksym K[1], Spencer R[1,3], Peebles DM[1,10], Buquis G[1], Ambler G[1], Morsing E[4], Ley D[4], Singer D[5], Tenorio V[6], Dyer J[1], Ginsberg Y[1,7], Weissbach T[1,8], Huertas-Ceballos A[9], Marlow N[1], David AL[1,10] on behalf of the EVERREST consortium

1. UCL Elizabeth Garrett Anderson Institute for Women's Health, University College London, United Kingdom
2. Neonatal Unit, West Hertfordshire NHS Trust, United Kingdom
3. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
4. Department of Paediatrics, Lund University, Lund, Sweden
5. Division of Neonatology and Pediatric Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
6. Institut D'Investigacions Biomèdiques August Pi í Sunyer, University of Barcelona, Barcelona Center for Maternal-Fetal and Neonatal Medicine, Barcelona, Spain
7. Department of Obstetrics and Gynecology, Rambam Medical Centre, Haifa, Israel
8. Department of Obstetrics and Gynecology, Sheba Tel Hashomer Hospital, Tel Aviv, Israel
9. Neonatal Unit, University College London Hospital NHS Foundation Trust, London, United Kingdom
10. National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom

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Abstract

Objective: To quantify the risks of mortality, morbidity and postnatal characteristics associated with extreme preterm fetal growth restriction (EP-FGR).

Design: EVERREST prospective multi-centre study of women diagnosed with EP-FGR (singleton, estimated fetal weight (EFW) <3rd centile, <600g, 20-26^{+6} weeks of gestation, NCT02097667). The UK sub-group of EP-FGR infants (<36 weeks) were sex and gestation-matched to appropriate for age (AGA) infants born in University College London Hospital (1:2 design, EFW 25^{th}-75th centile).

Setting: Four tertiary perinatal units (UK, Germany, Spain, Sweden)

Main outcomes: Antenatal and postnatal mortality, bronchopulmonary dysplasia (BPD), sepsis, surgically-treated necrotising enterocolitis (NEC), treated retinopathy of prematurity (ROP).

Results: Of 135 mothers recruited with EP-FGR, 42 had a stillbirth or termination of pregnancy (31%) and 93 had livebirths (69%). Post-natal genetic abnormalities were identified in 7/93 (8%) livebirths. Mean GA at birth was 31.4 weeks (SD 4.6). 54 UK-born preterm EP-FGR infants (<36 weeks) were matched to AGA controls. EP-FGR was associated with increased BPD (43% vs 26%, OR 3.6, 95%CI 1.4-9.4, p=0.01), surgical NEC (6% vs 0%, p=0.036) and ROP treatment (11% vs 0%, p=0.001). Mortality was probably higher amongst FGR infants (9% vs 2%, OR 5.0, 95%CI 1.0-25.8, p=0.054). FGR infants more frequently received invasive ventilation (65% vs 50%, OR 2.6, 95%CI 1.1-6.1, p=0.03), took longer to achieve full feeds and had longer neonatal stays (median difference 6.1 days, 95%CI 3.8-8.9 and 19 days, 95%CI 9-30 days respectively, p<0.0001).

Conclusions: Mortality following diagnosis of EP-FGR is high. Survivors experience increased neonatal morbidity compared to AGA preterm infants.

What we know on this subject

- EP-FGR is associated with increased risk of preterm associated complications
- EP-FGR is relatively uncommon and there are few published data about the postnatal course of these infants compared to appropriate weight for gestational age (AGA) infants.

What this study adds

- Compared to AGA infants, EP-FGR infants have a higher risk of respiratory morbidity, surgical NEC and treatment for retinopathy of prematurity.
- Infants with EP-FGR experience a prolonged duration of ventilation, delayed establishing of enteral feeds, poor postnatal growth and delayed discharge compared to gestational age – matched AGA infants.

How this study might affect research, practice or policy

– This study provides valuable data to inform antenatal counselling following diagnosis of EP-FGR and set healthcare practitioner and parental expectations for the challenges ahead.

INTRODUCTION

Fetal growth restriction (FGR) affects 1.46 million fetuses worldwide annually, contributing to approximately 30% of stillbirths [1]. FGR is defined as early-onset when identified before 32 weeks of gestation [2] and is predominately due to placental insufficiency in the absence of chromosomal, genetic or structural anomalies [3]. Currently, there are no interventions to improve *in-utero* growth [4]. Antenatal management provides active surveillance of fetal and maternal wellbeing, balancing risks of prematurity against *in-utero* exposure to chronic hypoxia, suboptimal nutrition, and risk of fetal death. Prematurity complications are inversely proportional to gestation, with greatest risk of death, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), sepsis and retinopathy of prematurity (ROP) at extreme preterm gestations [5,6]. Adverse sequelae may be exacerbated by FGR [7,8], but few studies have quantified these risks or characterised the postnatal course of affected infants, particularly those with early-onset FGR.

A systematic review of perinatal mortality and morbidity in FGR identified wide variability in diagnostic criteria [8]. Most included studies were small, retrospective, or observational with few reporting detailed neonatal outcomes. One large, well designed multi-centre randomised control trial (TRUFFLE) reported neonatal outcomes in infants with early-onset FGR diagnosed from 26-31^{+6} weeks of gestation [9]. Lower gestation at study entry and birth were strongly related to adverse outcomes; almost one third of infants had severe morbidity or died.

With the aim of developing a novel drug intervention to improve fetal growth *in-utero,* the EVERREST consortium prospectively recruited a cohort of singleton pregnancies diagnosed with FGR between 20^{+0}-26^{+6} weeks of gestation [10], a more extreme preterm FGR (EP-FGR) cohort compared to the TRUFFLE study. This provides a unique opportunity to characterise maternal, fetal and neonatal progress in EP-FGR. Here, we prospectively quantified the risks of mortality and neonatal morbidity among fetuses with EP-FGR identified before 27 weeks

gestation. To determine any additional risks of preterm-associated morbidity, we compared the UK-born EP-FGR infants to gestational-age and sex-matched appropriately grown (AGA) preterm infants in a nested case-control study.

METHODS

Setting

The EVERREST study was conducted in 4 centres; University College Hospital London (UCLH, United Kingdom), University Medical Center Hamburg-Eppendorf (Germany), Maternal-Fetal Unit Hospital Clinic de Barcelona (Spain) and Lund University Hospital (Sweden). The nested case-control study involved UK-born infants with pregnancies booked in UCLH, a tertiary referral centre for North Central and East London Neonatal Operational Delivery Network.

Participants

We recruited women with a live singleton fetus, estimated fetal weight, EFW<600g and <3rd centile [11,12] and gestation at EP-FGR diagnosis 20^{+0}-26^{+6} weeks, based on ultrasound and/or last menstrual period, to the EVERREST prospective study [10]. FGR was defined as EFW <3^{rd} centile [2], though gestation and weight limits were applied as fetuses >27 weeks or >600g may benefit from imminent delivery rather than trial participation. EFW was calculated using the Hadlock 3 formula and Marsal chart [12,13].

Participants gave written informed consent. Exclusion criteria included multiple pregnancy, age <18 years, maternal HIV, hepatitis B/C, cytomegalovirus infection (CMV), premature prelabour rupture of membranes (PPROM) before enrolment, immediate indication for delivery and known fetal genetic/structural abnormality. We excluded women who lacked capacity to give informed consent.

Decisions to deliver were in keeping with Royal College of Obstetrics and Gynaecology (RCOG) guidance [14] and published work by Marsal and Figueras & Gratacos [15]. Fetal monitoring was consistent across centres, though individual delivery decisions were multidisciplinary, following discussion with the patient, obstetrician, and neonatologist.

Matching process

EP-FGR patients were consecutively recruited between June 2014-April 2020. EP-FGR infants born <36 weeks' gestation in UK-centres were matched to AGA infants (1:2 design) on gestational age (GA) and sex. AGA infants were selected using a random number generator from a database of neonatal admissions between January 2013-December 2018, filtered by sex, gestation (weeks) and birthweight (25^{th}-75^{th} centile; UK-WHO Neonatal and Infant Monitoring Growth Chart). EP-FGR infants enrolled in the UK received their antenatal care in UCLH. The majority (76%,41/54) were born in ULCH, though 24% (13/54) delivered in their local hospital. AGA infants received all antenatal and postnatal care at UCLH.

EVERREST Study Outcomes (Multi-centre)

Main outcomes were overall mortality from diagnosis of EP-FGR (antenatal and postnatal), neonatal death before discharge and severe neonatal co-morbidities, including moderate or severe BPD (receiving oxygen or non-invasive respiratory support at 36 weeks postmenstrual age), sepsis (positive blood culture, excluding contaminants), treatment for ROP, necrotising enterocolitis requiring surgery ("surgical NEC") and focal brain injury (IVH distending lateral ventricles (Papile grade III), haemorrhagic parenchymal infarcts or ventricular dilatation requiring shunt placement). We calculated an overall composite of death or any of the above severe morbidities.

EP-FGR vs AGA matched infants born <36 weeks (UK-only)

For the subgroup of EP-FGR and matched AGA infants born <36 weeks gestation at UCLH, a range of maternal variables were collected according to the Global Pregnancy Collaboration (CoLab) minimum data set [16], in addition to neonatal mortality, morbidities, and postnatal characteristics. We defined pregnancy-induced hypertension as blood pressure (BP) >140/90 after 20 weeks gestation in the absence of pre-eclampsia, and pre-eclampsia as hypertension with proteinuria, organ dysfunction or uteroplacental dysfunction [17].

Postnatal infant characteristics included the receipt and duration of invasive ventilation (minimum 6 hours), duration of invasive and non-invasive ventilation, duration of supplemental oxygen, time to reach full enteral feeds (150ml/kg/day), duration of parenteral nutrition (PN), total duration kept nil by mouth (NBM), ROP (any stage), NEC (Bells Stage IIA or above [18]), Patent Ductus Arteriosus (PDA) ligation/device closure, PDA requiring medical treatment, all sepsis (proven and suspected sepsis, defined as unwell with raised inflammatory markers and received >5 days intravenous (IV) antibiotics) and length of stay. Intestinal dysmotility was defined as withholding feeds >12 hours in the first 2 weeks of life due to abdominal distention and/or bilious aspirates with no evidence of sepsis or NEC. Episodes of NEC and sepsis were independently evaluated by 2 neonatologists (IL, AH) to achieve consensus. Weight z-scores [19] were calculated for birthweight and weight at 36 weeks postmenstrual age (if weight at 36 weeks was unavailable, discharge weight was used if performed between 34-38 weeks corrected GA).

Statistics

Statistical analysis was performed in Stata 16 and Prism v8.0.0 [20,21]. Numerical outcomes were analysed with parametric or non-parametric tools as appropriate. Skewed data was log-transformed before modelling. Binary outcomes were analysed with conditional regression and numerical outcomes with mixed modelling, maintaining 1:2 pairings. Pairings with missing data were excluded. Conditional regression was not possible for rare outcomes, therefore analysed unpaired using logistic regression (adjusting for FGR, sex, gestation) or Fisher's

exact test. As cohorts were not randomised, unpaired analysis should be interpreted with caution.

Research Governance

The EVERREST study was approved by the London-Stanmore Research Ethics Committee (13/LO/1254) and registered on ClinicalTrials.gov (NCT02097667). UCLH Clinical Governance approved using anonymised, routine clinical data from AGA infants to inform antenatal counselling as a quality improvement project; ethical approval was waived.[22]

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RESULTS

EVERREST cohort (Multi-centre)

The EVERREST cohort comprised 135 women with EP-FGR (excluding 2 mothers who did not meet inclusion criteria, 1 with congenital CMV and 4 who withdrew),(Figure 1). Antenatal mortality was 31% (42/135), comprising 35 stillbirths and 7 terminations. Data from 93 livebirths were analysed.

Mean gestation at birth was 31.4 weeks (S.D. 4.6) with a mean birth weight 1149 grams (S.D. 693) and birth weight z-score -2.53 (S.D. 0.64),(Table 1). Almost 80% of infants (74/93) were born preterm (<37 weeks' gestation); 85% (79/93) were admitted to a neonatal unit. One infant died following planned palliative care (24 weeks' gestation, birth weight 295g). Postnatal

mortality was 13% (12/93) and 39% (36/93) survived with major neonatal morbidity, predominately BPD (30/93) and sepsis (10/93).

Most postnatal deaths occurred in infants <29 weeks gestation (9/11) and within one month of life (Figure 2A), predominately from respiratory causes (n=6). Other causes of death included multi-organ failure (n=2), sepsis (n=1), NEC (n=1), planned palliative care due to severe EP-FGR (n=1) and following diagnosis of Trichothiodystrophy (n=1).

Genetic syndromes were identified in 8% (7/93) infants after birth: Russell-Silver syndrome (n=2), Trichothiodystrophy (n=1), Diamond-Blackfan anaemia (n=1) and Tetrasomy 9p (n=1), chromosomal deletion/duplication on micro-array (n=2).

EP-FGR vs AGA matched infants born <36 weeks' gestation (UK-only)

Of the 73 EP-FGR infants enrolled to the EVERREST in the UK, 63 were admitted to the neonatal unit and 3 were admitted to transitional care and/or postnatal ward. There were 54 EP-FGR babies born <36 weeks gestation matched to 108 UCLH-born AGA infants. Sensitivity analysis of UCLH-only EP-FGR infants did not significantly alter findings (Appendix_1).

Mean GA at birth for infants in both groups was 30.0 weeks (SD 2.9) (Appendix_2). Mean birth weight z-scores reflected study entry criteria (EP-FGR: -2.53 (SD 0.64), AGA: -0.27 (SD 0.54)). There was no significant difference in exposure to antenatal steroids or magnesium sulphate. Among EP-FGR infants 51/54 (94%) were delivered by caesarean section compared with 48/108 (44%) AGA infants ($p<0.01$). Measures of condition at birth were similarly distributed (Table 2). Overall, 27/54 (50%) EP-FGR infants had the composite poor neonatal outcome compared with 31/108 (29%) AGA infants (OR 5.0, 95%CI 1.8-13.9,$p<0.0001$).

Antenatal and Perinatal Background

Maternal hypertension (any cause) was more prevalent in EP-FGR pregnancies, while PPROM, maternal sepsis and chorioamnionitis were more common in AGA. Adjusting for EP-FGR status, maternal hypertension was the only antenatal factor independently associated with composite poor neonatal outcome (OR 5.2, 95%CI 1.2-22.1,p=0.026).

Mortality and Neonatal Morbidity

Overall neonatal mortality of babies born in the UK was 7% (5/73). Comparing the subset of preterm infants < 36 weeks admitted to a neonatal unit, inpatient mortality was probably higher in the EP-FGR group (5/54 (9%)) compared to 2/108 (2%) of AGA infants (OR 5.0, 95%CI 0.97-25.8, p=0.054). BPD was the most common neonatal morbidity. EP-FGR significantly increased the odds of supplemental oxygen or non-invasive respiratory support at 36 weeks PMA (OR 3.6, 95%CI 1.4–9.4,p=0.01). Surgical NEC occurred only in EP-FGR infants (6% vs 0%,p=0.036), as did treatment for ROP (11% vs 0%,p=0.001). Severe brain injury was only present in 3 AGA infants (0% vs 3%,p=0.55). Rates of proven sepsis were similar in both groups. Major morbidities largely occurred in infants born <30 weeks (Table 3). Clinical and biochemical data are included in Appendix_3.

Postnatal characteristics

EP-FGR infants experienced a more complex respiratory course than AGA infants. Invasive ventilation was prolonged amongst EP-FGR infants born <30 weeks (median 23 days, IQR 2-46 vs 2 days, IQR 1-7,p<0.0001), with increased exposure to postnatal steroids (OR 38.3, 95%CI 5.9-247,p<0.0001) and medical PDA management (OR 13.1, 95%CI 1.6–107,p=0.016).

Establishing enteral feeds proved challenging in EP-FGR infants who took 6.1 days longer to reach 150ml/kg/day (16 days, IQR 11-20 vs 10 days, IQR 8-13,p<0.0001) (Figure 2),

increasing the duration of PN (15 days, IQR 9–26; AGA: 8 days, IQR 0-12,p<0.0001)(Table 3).

The more complex neonatal course for EP-FGR infants resulted in delayed discharge compared to AGA, by 19 days (95%CI 9-30 days,p=0.0001) overall and 36 days (95%CI 8-75 days,p=0.009) among those born <30 weeks. Furthermore, 36 week/discharge weight was lighter following EP-FGR. In those born <30 weeks, the EP-FGR group had discharge weight z-scores 2.3 SD (95% CI 2.0-2.7,p=0.001) lower than AGA controls.

Discussion

We studied mortality and morbidity associated with extreme preterm fetal growth restriction (EP-FGR, EFW<3rd percentile and <600g) to evaluate the neonatal effects of poor fetal growth identified before 27 weeks of gestation. Overall mortality from diagnosis was high, predominately due to stillbirths. Neonatal mortality, in contrast, was relatively low among preterm births, despite the significantly lower birthweight for gestation. EP-FGR was associated with a more complex neonatal course compared with appropriately grown infants, and specifically, with increased risks of moderate/severe BPD, surgical NEC and ROP requiring treatment. Postnatally, EP-FGR infants experienced a more complex and lengthier inpatient stay with increased ventilatory requirements, delays in establishing enteral feeds and suspected sepsis. This increased risk of complex major morbidities may translate into poorer neurodevelopmental outcome in childhood.

Whilst FGR is known to adversely influence postnatal outcomes, little data exist to quantify this additional risk compared to preterm birth alone, making antenatal counselling challenging. We observed an increased mortality in EP-FGR infants, of marginal significance. Neonatal mortality was higher (9%) than previously observed in the TRUFFLE study (5.5%) probably due to the earlier gestation at diagnosis of EP-FGR in our EVERREST cohort (<3rd centile, 20-

26+6 weeks) compared to later, less severe TRUFFLE study phenotype (<10th centile from 26–32 weeks GA) [6]. In fact, 25 women recruited to EVERREST had a stillbirth or preterm delivery under 26 weeks GA, therefore would not have been eligible to participate in TRUFFLE.

EP-FGR infants experienced increased respiratory morbidity requiring more intensive and invasive neonatal interventions, including prolonged mechanical ventilation, PDA management and steroid exposure, culminating in an increased risk of BPD. We observed greater proportions of EP-FGR infants with BPD (33%) compared to other FGR cohorts, in whom reports suggest a risk of 10–20% [8,9,23], which reflects the early gestational age at onset of FGR in this population. Aetiology is likely multifactorial; placental insufficiency and chronic fetal hypoxia are associated with altered pulmonary micro-architecture, impaired alveolarisation and reduced surfactant protein gene expression [24–26]. Altered pulmonary structural development is primarily observed in early rather than late-onset FGR [7] and may explain the poor outcomes in this cohort.

Comparing preterm EP-FGR to AGA infants, we observed a 10-fold increase in odds of NEC (Bells stage IIA and above), and strong association with the need for surgery. This may be attributed to chronic fetal hypoxic-ischaemic gut injury, impairing the motor, secretory and mucosal function [27]. NEC (confirmed and suspected cases) was more common in EP-FGR compared to AGA infants, possibly reflecting their clinical instability and/or hypervigilance for NEC. Poor growth persisted postnatally with most EP-FGR infants having a lower weight z-score at 36 weeks' gestation or discharge compared to birth; both a symptom and contributor to increased morbidity. We also observed a strong association of ROP treatment and EP-FGR, consistent with published data [28]. The aetiology could be a combination of increased respiratory requirements, postnatal growth failure and altered microvascular development [28,29]. These three major neonatal morbidities (BPD, NEC, ROP) may share a common pathology involving microvascular/microcirculatory maladaptation to FGR.

This study included pregnancies affected by EP-FGR across four perinatal centres, both a strength and limitation. including of all neonatal data may provide some translatability given the national and international variability in neonatal practice, though comparisons made to AGA infants exclusively relates to practice in a single UK centre. This study evaluated infants with EP-FGR; outcomes of infants with late-onset FGR or small for gestational age may differ.

In conclusion, EP-FGR infants experience a protracted neonatal stay, complicated by respiratory, nutritional, and infective complications. This is valuable data to inform antenatal counselling and help set healthcare practitioner and parental expectations for the challenges ahead.

Contribution Statement

UK data collection was undertaken by IL,JO,GB,RS,KM (European data collection led by EM,DL,DS,VT,YG,TW). Analysis was performed by IL,RS,GA. The manuscript was drafted by IL and reviewed by JO,RS,KM,GA,DP,AHC,NM,AD. All co-authors approved the final manuscript.

REFERENCES

1 Lawn JE, Blencowe H, Pattinson R, *et al.* Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011;**377**:1448–63. doi:10.1016/S0140-6736(10)62187-3

2 Gordijn SJ, Beune IM, Thilaganathan B, *et al.* Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound in Obstetrics & Gynecology* 2016;**48**:333–9. doi:10.1002/uog.15884

3 Lackman F, Capewell V, Gagnon R, *et al.* Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. *Am J Obstet Gynecol* 2001;**185**. doi:10.1067/mob.2001.116686

4 Nawathe A, David AL. Prophylaxis and treatment of foetal growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2018;**49**:66–78. doi:10.1016/j.bpobgyn.2018.02.007

5 Costeloe K, Hennessy E, Gibson AT, *et al.* The EPICure study: Outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics* Published Online First: 2000. doi:10.1542/peds.106.4.659

6 Costeloe KL, Hennessy EM, Haider S, *et al.* Short term outcomes after extreme preterm birth in England: Comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ (Online)* Published Online First: 2012. doi:10.1136/bmj.e7976

7 Malhotra A, Allison BJ, Castillo-Melendez M, *et al.* Neonatal Morbidities of Fetal Growth Restriction: Pathophysiology and Impact. *Front Endocrinol (Lausanne)* 2019;**10**:55. doi:10.3389/fendo.2019.00055

8 Pels A, Beune IM, van Wassenaer-Leemhuis AG, *et al.* Early-onset fetal growth restriction: A systematic review on mortality and morbidity. Acta Obstet Gynecol Scand. 2020. doi:10.1111/aogs.13702

9 Lees C, Marlow N, Arabin B, *et al.* Perinatal morbidity and mortality in early-onset fetal growth restriction: Cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound in Obstetrics and Gynecology* Published Online First: 2013. doi:10.1002/uog.13190

10 Spencer R, Ambler G, Brodszki J, *et al.* EVERREST prospective study: a 6-year prospective study to define the clinical and biological characteristics of pregnancies affected by severe early onset fetal growth restriction. *BMC Pregnancy Childbirth* 2017;**17**:43. doi:10.1186/s12884-017-1226-7

11 Maršál K, Persson P-H, Larsen T, *et al.* Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr* 1996;**85**:843–8. doi:10.1111/j.1651-2227.1996.tb14164.x

12 Hadlock FP, Harrist RB, Sharman RS, *et al.* Estimation of fetal weight with the use of head, body, and femur measurements—A prospective study. *Am J Obstet Gynecol* 1985;**151**:333–7. doi:10.1016/0002-9378(85)90298-4

13 Maršál K. Obstetric management of intrauterine growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2009;**23**:857–70. doi:10.1016/j.bpobgyn.2009.08.011

14 Royal College of Obstetricians & Gynaecologists. Green-top Guideline No.31: The Investigation and Management of the Small–for–Gestational–Age Fetus. *Green-top Guideline No31* 2013.

15 Figueras F, Gratacós E. Update on the Diagnosis and Classification of Fetal Growth Restriction and Proposal of a Stage-Based Management Protocol. *Fetal Diagn Ther* 2014;**36**:86–98. doi:10.1159/000357592

16 Myatt L, Redman CW, Staff AC, *et al.* Strategy for Standardization of Preeclampsia Research Study Design. *Hypertension* 2014;**63**:1293–301. doi:10.1161/HYPERTENSIONAHA.113.02664

17 National Institute for Health and Care Excellence (NICE 2019). Hypertension in pregnancy: diagnosis and management [NG 133]. https://www.nice.org.uk/guidance/ng133 (accessed 22 Nov 2021).

18 Walsh MC, Kliegman RM. Necrotizing Enterocolitis: Treatment Based on Staging Criteria. *Pediatr Clin North Am* 1986;**33**:179–201. doi:10.1016/S0031-3955(16)34975-6

19 Cole TJ, Freeman J v., Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med* 1998;**17**. doi:10.1002/(SICI)1097-0258(19980228)17:4<407::AID-SIM742>3.0.CO;2-L

20 GraphPad Prism. GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. 2018.

21 StataCorp. Stata Statistical Software: Release 15. College Station: TX: StataCorp LLC: 2017. Scientific Research. 2017;**04**.

22 von Elm E, Altman DG, Egger M, *et al.* The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *International Journal of Surgery* 2014;**12**. doi:10.1016/j.ijsu.2014.07.013

23 Groom KM, McCowan LM, Mackay LK, *et al.* STRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. *BJOG* 2019;**126**. doi:10.1111/1471-0528.15658

24 Rozance PJ, Seedorf GJ, Brown A, *et al.* Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction in vitro in fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2011;**301**. doi:10.1152/ajplung.00197.2011

25 Orgeig S, Crittenden TA, Marchant C, *et al.* Intrauterine growth restriction delays surfactant protein maturation in the sheep fetus. *Am J Physiol Lung Cell Mol Physiol* 2010;**298**. doi:10.1152/ajplung.00226.2009

26 Gortner L, Hilgendorff A, Bähner T, *et al.* Hypoxia-induced intrauterine growth retardation: Effects on pulmonary development and surfactant protein transcription. *Biol Neonate* 2005;**88**. doi:10.1159/000085895

27 Dorling J, Kempley S, Leaf A. Feeding growth restricted preterm infants with abnormal antenatal Doppler results. Arch Dis Child Fetal Neonatal Ed. 2005;**90**. doi:10.1136/adc.2004.060350

28 Chu A, Dhindsa Y, Sim MS, *et al.* Prenatal intrauterine growth restriction and risk of retinopathy of prematurity. *Sci Rep* 2020;**10**. doi:10.1038/s41598-020-74600-0

29 Hartnett ME, Penn JS. Mechanisms and Management of Retinopathy of Prematurity. *New England Journal of Medicine* 2012;**367**. doi:10.1056/nejmra1208129

Table 1. Mortality and Morbidity of infants with EP-FGR (EVERREST Cohort, Multi-centre)

Outcomes of EVERREST Cohort n = 135	n, %	Comments
Overall mortality	54 (40)	***Breakdown of postnatal deaths:***
- Antenatal		23/40 (n=1), age 15 days
- Termination of Pregnancy	7 (5)	24/40 (n=2), age 0 days (palliation after birth), age 5 days
- Intra-uterine Death	35 (26)	25/40 (n=1), age 2 days
		26/40 (n=3), age 3 days; 27 days; 223 days
- Post-natal death (from diagnosis of EP-FGR)	12 (9)	27/40 (n=1), age 10 days
		28/40 (n=2), age 17 days; 288 days
		31/40 (n=1), age 28 days
		37/40 (n=1), age 97 days
Total Live births	93 (68)	
Male	41 (45)	
Mean GA at birth, weeks (S.D.)	31.4 (4.6)	
Mean BW, grams (S.D.)	1149 (693)	
Mean z-score (S.D.)	-2.53 (0.64)	
GA at birth (weeks)		
- 22+0 – 25+6	9 (10)	
- 26+0 – 29+6	34 (37)	
- 30+0 – 33+6	21 (23)	
- 34+0 – 36+6	10 (11)	
- 37+0 and above	19 (20)	
Admitted to a neonatal unit	79 (85)	
Neonatal death (after live-birth)	12 (13)	****Confirmed genetic syndromes:***
BPD	30 (32)	
Surgical NEC	3 (3)	Russel-silver syndrome, (n=2)
ROP Treatment	6 (6)	Trichothiodystrophy (n=1)
Sepsis	10 (11)	Diamond-Blackfan anaemia (n=1)
Focal brain injury	1 (1)	Tetrasomy 9p (n=1)
		Chromosome 20p deletion (clinically significant), (n=1)
Survivors with major neonatal morbidity (GA < 37+0 weeks)	36 (39)	22q11.22q duplication (uncertain significance), (n=1)
Post-natal genetic diagnosis*	7 (8)	

GA= gestation age, BW= birthweight, S.D.=standard deviation, BPD= Bronchopulmonary dysplasia, NEC= necrotising enterocolitis, ROP= retinopathy of prematurity

Table 2. Neonatal, Antenatal and Intrapartum characteristics of infants under 36 weeks' GA (UK-Cohort)

	EP-FGR n=54	AGA n=108	p-value
Neonatal			
Gestation at birth (weeks) (mean, S.D)	30.0 (2.9)	30.0 (2.9)	
Gestation at birth (n,%) - 25+0 – 29+6 - 30+0 – 35+6	 28 (52) 26 (48)	 56 (52) 52 (48)	
Sex (n,%) - Male - Female	 22 (41) 32 (59)	 44 (41) 64 (59)	
Antenatal			
Antenatal steroids (GA < 34 weeks), (n,%) - Full course - Incomplete course - No steroids	 49/54 (91) 4/54 (7) 0/54 1/54 (2)	 80/108 (83) 11/108 (12) 5/108 (5) 0	 0.79 >0.99
Pregnancy-induced hypertension (n,%)	7/54 (13)	9/108 (8)	**0.0349**
Pre-eclampsia (n,%)	16/54 (30)	8/108 (7)	**0.0001**
Maternal hypertension (any cause) (n,%)	20/54 (30)	10/108 (9)	**0.0002**
Gestational diabetes (n,%) [f]	2/54 (4)	8/108 (7)	0.498
Placenta previa (n,%) [f]	0/54(0)	4/108 (4)	0.302
Maternal thyroid abnormality (n,%)	4/52 (8)	9/108 (8)	0.838
Antepartum haemorrhage	4/54 (7)	24/108 (4)	1.0
Risk factors for sepsis (GBS positive, PPROM, maternal sepsis or chorioamnionitis)	4/54 (7)	63/108 (58)	**>0.0001**
Perinatal			
Magnesium sulphate (GA<30 weeks) (n,%) - Given - Not given - Not documented	 21/28 (75) 7/28 (25) 0	 37/108 (66) 18/108 (32) 1/108 (2)	 0.46 >0.99
Placental abruption (n,%)	2/54 (4)	2/108 (2)	1.0
Mode of delivery (n,%) - Emergency LSCS - Elective LSCS (Cat4) - Normal vaginal delivery	 51/54 (94) 2/54 (4) 1/54 (2)	 48/108 (44) 9/108 (8) 51/108 (47)	 0.38
Postnatal			
Apgar scores (median, IQR) - 1 min - 5 min	 6 (3-8), n=51 8 (7-9), n=51	 7 (4-9), n=101 9 (7-9) , n=101	 0.91
Arterial Cord pH (median, IQR) [m]	7.24 (7.19-7.29) n=27	7.22 (7.16-7.33), n=39	0.901
Birth weight (g), (Mean, S.D)	902 (378)	1425 (489)	
Birth weight z-score, (Mean, S.D)	-2.53 (0.64)	- 0.27 (0.54)	

Statistical analysis conditional regression unless otherwise specified (f = fishers exact test, m = mixed modelling). GBS = Group B Streptococcus, PPROM = preterm prolonged rupture of membranes, GA = gestational age, LSCS = Lower segment caesarean section, IQR = interquartile range, IQR=interquartile range, S.D.=standard deviation

Table 3. Neonatal mortality, morbidity and postnatal clinical characteristics of EP-FGR compared to AGA infants born under 36 weeks' GA (UK-Cohort)

	UK Total Cohort (<36 weeks)			GA 25+0 – 29+9			GA 30+0-35+6		
	EP-FGR n=54	**AGA n=108**	**OR (95%CI)**	**EP-FGR n=28**	**AGA n=56**	**OR (95%CI)**	**EP-FGR n=26**	**AGA n=52**	**OR (95%CI)**
Mortality and Major Morbidity (n%)									
Mortality	5 (9)	2 (2)	5.0 (1.0 – 25.8)	4 (14)	2 (4)	3.5 (0.7-21.8)	1 (4)	0	
Bronchopulmonary dysplasia	23 (43)	28 (26)	**3.6 (1.4-9.4)**	21 (75)	24 (43)	**6.1 (1.7-21.9)**	2 (8)	4 (8)	1.0 (0.2-5.5)
Proven Sepsis	6 (11)	5 (5)	2.7 (0.8-9.7)	6 (21)	5 (9)	2.7 (0.8-9.7)	0	0	
ROP requiring treatment	6 (11)	0 (0)	-	6 (21)	0 (0)	-	0	0	
Surgical NEC	3 (6)	0 (0)	-	3 (11)	0 (0)	-	0	0	
Severe IVH, PVL or PHVD	0 (0)	3 (3)	-	0 (0)	2 (4)	-	0	1 (2)	
Composite neonatal mortality and morbidity	27 (50)	31 (29)	**5.0 (1.8-13.9)**	24 (86)	26 (46)	**10.7 (2.4-47.8)**	3 (12)	5 (10)	1.3 (0.2-6.9)
Post-natal Clinical Characteristics									
Respiratory									
Need for invasive ventilation	35 (65)	54 (50.0)	**2.6 (1.1–6.1)**	25 (89)	44 (79)	2.7 (0.6-12.8)	10 (39)	10 (19)	2.5 (0.9-7.1)
Received curosurf	36 (67)	60 (55.6)	3.0 (1.0 to 8.9)	27 (96)	51 (91)	2.9 (0.3-27.9)	9 (35)	9 (17)	3.0 (0.9-10.4)
Postnatal steroid exposure	13 (24)	4 (4)	**38.3 (5.9-247.2)**	13 (46)	4 (7.)	**36.0 (5.7-238.8)**	0	0	-
Received iNO in first week of life	3 (6)	2 (2)	3.0 (0.5-17.9)	3 (11)	2 (4)	3.0 (0.5-17.9)	0	0	-
Cardiovascular									
PDA ligation	1 (2)	0 (0)		1 (3)	0 (0)		0	0	-
PDA medical management	10 (19)	4 (4)	**13.6 (2.8-66.1)**	10 (36)	4 (7)	**12.4 (2.7-58.1)**	0	0	-
Gastro-intestinal									

Enteral feeds commenced										
- within 12h	12 (22)	27 (25)	1.0		2 (7)	8 (14)	1.0		10 (38)	19 (37)	1.0
- between 12 – 24h	17 (32)	31 (29)	1.3 (0.5-3.5)		11 (39)	14 (25)	3.3 (0.6-18.0)		6 (23)	17 (33)	0.7 (0.2-2.5)
- after 24h	25 (46)	49 (45)	1.3 (0.5-3.3)		15 (54)	33 (59)	2.1 (0.4-11.5)		10 (38)	16 (31)	1.2 (0.4-4.1)
Type of milk during admission										
- Exclusively breast milk	11 (20)	30 (28)	1.0		22 (79)	21 (38)	1.0		7	9 (17)	1.0
- > 50% breast milk	15 (28)	31 (29)	1.4 (0.5-3.6)		5 (18)	13 (23)	3.7 (0.9-14.6)		6	18 (35)	0.3 (0.1-1.6)
- Mixed feeding	20 (37)	34 (32)	1.6 (0.7-4.0)		1 (4)	16 (29)	3.0 (0.9-10.7)		10	18 (35)	0.6 (1.4-2.5)
- > 50% preterm formula	6 (11)	10 (9)	1.8 (0.5-5.8)		0 (0)	5 (9)	5.8 (0.9-36.3)		2	5 (10)	0.6 (0.1-3.5)
- Exclusively formula milk	1 (2)	2 (2)	1.3 (0.1-16.6)		0 (0)	0 (0)			1	2 (4)	0.4 (0.03-6.3)
Dysmotility in first 2 weeks of life	6 (11)	9 (8.3)	1.8 (0.6-5.7)		3 (11)	6 (11)	1.6 (0.3-8.4)		3 (12)	3 (6)	2.0 (0.4-9.9)
NEC (stage IIA or above)	6 (11)	1 (2)	**12 (1.4-99.7)**		6 (21)	1 (2)	**12 (1.4-99.7)**		0	0	-
Suspected NEC	13 (24)	4 (4)	**11.6 (2.6–51.7)**		10 (36)	4 (7)	**8.6 (1.9-39.7)**		3 (12)	0	-
Other											
Any sepsis (including presumed sepsis)	33 (61)	21 (19)	**12 (3.8–42)**		23 (82)	15 (27)	**9.9 (2.9-33.8)**		0	6 (12)	
IVH (any grade)	10 (19)	21 (19)	0.8 (0.3 – 2.0)		8 (29)	20 (36)	0.7 (0.3-1.9)		2 (8)	1 (2)	4.3 (0.4-50.2)
ROP (grade 2 or above)[S]	15 (28)	6 (6)	**16.5 (4.2-65.8)**		15 (54)	6 (11)	**14.9 (3.9-56.9)**		0	0	
	EP-FGR n=54	**AGA n=108**	**Difference (95%CI)**		**EP-FGR n=28**	**AGA n=56**	**Difference (95%CI)**		**EP-FGR n=28**	**AGA n=56**	**Difference (95%CI)**
Respiratory											
Duration of invasive ventilation (median days, IQR)	2 (0-23.8)	0 (0-2.0)	**3.01 (1.70-4.81)**		23 (2-45.5)	2 (1-7)	**11.0 (5.4-20.6)**		0 (0-1.8)	0 (0-0)	0.9 (0.2-1.7)
Duration of invasive and non-invasive ventilation (median days, IQR)	25.5 (6.3-78)	10.5 (2.0-48.3)	**10.2 (5.4-16.5)**		78 (41-116.5)	47.5 (21.75-60.25)	**36.5 (15.4-66.2)**		5.5 (1.3-17.3)	2 (0-4)	2.5 (0.8-5.3)
Total oxygen therapy (median days, IQR)	31.5 (7.0-109.3)	16 (2.0-55.3)	**11.8 (6.1-19.4)**		107.5 (51-153.5)	51 (28-87.75)	**45.2 (18.5-83.2)**		6 (1.3-20.5)	2 (0-4)	2.7 (0.8-5.8)
Nutrition											
Time to reach 150ml/kg/d enteral feeds (median days, IQR)	16 (11-20)	10 (8-13)	**6.1 (3.8-8.9)**		19 (17-33)	13 (10.5-17)	**12.6 (7.0-19.8)**		10 (8-13)	8 (7-9)	2.1 (0.8-3.7)
Days kept NBM (median days, IQR)	3 (1-7)	1 (0-2)	**1.8 (1.1-2.6)**		6 (2.5-10)	2 (1-2.25)	**3.58 (1.86-6.10)**		1 (0-3.8)	1 (0-1)	0.7 (0.3-1.2)

Duration of parenteral nutrition (median days, IQR)	15 (8.8-26)	8 (0-12)	**7.8 (5.1-11.1)**		25 (16-31)	12 (10-16)	**13.2 (7.5-20.5)**		8 (0-11.8)	0 (0-0)	**4.0 (2.1-6.8)**
Weight at 36 weeks (mean, S.D)	1.5 (0.3)	2.2 (0.3)	-0.7 (-0.8 to -0.6)		1.4 (0.3)	2.3 (0.3)	-0.8 (-1.0 to -0.7)		1676 (284)	2191 (238)	-0.6 (-0.7 to -0.4)
Weight z-sore at 36 weeks or discharge home (mean, S.D)	-3.1 (0.8)	-1.0 (0.7)	**-2.0 (-2.3 to -1.8)**		-3.3 (0.8)	-0.9 (0.8)	**-2.3 (-2.7 to -2.0)**		-2.8 (0.7)	-1.1 (0.7)	-1.7 (-2.0 to -1.4)
Change in z-score from birth – 36 weeks or discharge (mean, S.D)	-0.6 (0.5)	-0.8 (0.6)	-		-0.7 (0.6)	-0.7 (0.6)	-		-0.4 (0.4)	-0.8 (0.4)	0.4 (0.2-0.6)
Other											
Length of stay (median days, IQR)[m]	68 (32.8-120.3)	52 (27-80.3)	**18.8 (8.9-30.5)**		119.5 (92-157)	79 (63-110)	**36.4 (7.8 74.6)**		36.5 (28-46.8)	27 (20-39)	**9.0 (4.3-14.5)**
Postnatal age at discharge (median weeks, IQR)	39.9 (37.6-43.1)	37.6 (36.3-39.1)	**4.0 (2.3-5.7)**		43.1 (41.5-50.6)	38.9 (37.1-42.5)	**6.9 (3.8-10.3)**		37.9 (37-39.3)	36.7 (36.0-37.6)	1.2 (0.5-1.9)

Statistical analysis conditional regression unless otherwise specified as s=standard regression, f=fishers exact test, m=mixed modelling. ROP= retinopathy of prematurity, NEC= necrotising enterocolitis, IVH=intraventricular haemorrhage, PVL= periventricular leukomalacia, PHVD= post-haemorrhagic ventricular dilatation, IQR= interquartile range, iNO= inhaled nitric oxide (first week of life), PDA= patent ductus arteriosus, NBM= nil by mouth.
Statistically Significant findings ($p<0.05$) highlighted in bold