Title: An investigation of the neonatal burden of disease of hypertensive disorders of pregnancy: a population-based study using the National Neonatal Research Database

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National Neonatal Research Database data extraction and data analyst support costs are being funded by the NIHR Research Professorship (Chappell, joint Chief Investigator). NIHR Research Professorship ref RP-2014-05- 019.

Protocol statement

This protocol describes the study. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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1 PLAIN ENGLISH SUMMARY

Around one in ten women have high blood pressure in pregnancy. This is potentially serious, with risks to the woman and her baby. Whilst maternal deaths from high blood pressure in pregnancy are now rare in the UK, blood pressure problems in pregnancy still cause many stillbirths and early births. Studies have shown that women of Black and Asian backgrounds are more likely to have worse pregnancy outcomes when blood pressure problems in pregnancy develop.

This study aims to:
i) describe the burden of disease of high blood pressure in pregnancy amongst babies admitted to neonatal units on a national scale.
ii) investigate outcomes for babies born to women with high blood pressure in pregnancy admitted to UK neonatal units across maternal ethnic groups.

To complete this study, we will use the National Neonatal Research Database, which holds population-level data for all babies admitted to neonatal units (where unwell babies receive care) in the UK. We will look at records of babies admitted to neonatal units in England and Wales between 2012 and 2020. The records will include information on over half a million babies and their mothers. We will assess how many babies admitted to neonatal units were born to women who had high blood pressure in pregnancy. We will report the outcomes of these babies, and how they compare to babies born to women without high blood pressure in pregnancy. We will analyse whether outcomes for babies born to women with high blood pressure in pregnancy varies according to maternal ethnicity, and investigate what may be driving differences we find.

We will work in partnership with women with lived experience of high blood pressure in pregnancy from a range of ethnic backgrounds and patient support charity Action on Pre-eclampsia (APEC) to interpret and share the findings of this study.

2 INTRODUCTION

Recent UK Maternal and Perinatal Death Confidential Enquiry reports have identified a greater risk of death in pregnant and postpartum women of Black, Asian and minority ethnic group backgrounds and their babies.[1,2] The reports have called for urgent investigation of ethnic disparities in maternal and perinatal morbidity.

Hypertensive disorders of pregnancy are one of the most common complications of pregnancy, affecting approximately one in ten pregnant women (≈70,000 women/year in the UK). This includes chronic (pre-existing) hypertension and new-onset hypertensive disorders such as gestational hypertension and pre-eclampsia. Whilst maternal deaths from hypertensive disorders of pregnancy are now rare in the UK following improvements in antenatal care and clinical management,[3] they continue to cause substantial perinatal morbidity and mortality including preterm birth, low birth weight and stillbirth. Pregnancy hypertension is thought to be responsible for 10-20% of preterm deliveries, and has an estimated stillbirth rate of 0.3-1.9% in high-income settings and up to 25% in low-income settings.[4–8] The incidence and risk of adverse outcomes of hypertensive disorders have repeatedly been demonstrated to vary significantly across maternal ethnic groups in high-income settings, with Black women at highest risk.[8–13]

This study will be the first to describe the national neonatal morbidity (including respiratory, gastrointestinal and central nervous system complications, together with hypoglycaemia which may be influenced by drug treatment for hypertension) and mortality of hypertensive disorders of pregnancy in babies admitted to neonatal units in the UK using a contemporaneous neonatal electronic health record cohort and investigate ethnic disparities in this cohort.

3 PATIENT AND PUBLIC INVOLVEMENT

Greater understanding of the neonatal morbidity and mortality of hypertensive disorders of pregnancy, particularly at preterm gestations, will address one of the recently published Top 10 research questions in pregnancy hypertension: "What is the best way to manage pregnancy hypertension… including timing of delivery?".[14] These priority research questions were co-developed with women with lived experience of pregnancy hypertension and public partners using a James Lind Alliance Priority Setting Partnership framework, led by join Chief Investigator Professor Chappell.

Given the potentially sensitive nature of the study findings with regard to maternal ethnicity (which is currently a highly topical subject in maternity care e.g. The Five X More Campaign), we will work with women with lived experience of high blood pressure in pregnancy from a range of ethnic backgrounds and relevant maternity groups and networks in order to achieve culturally sensitive interpretation and dissemination of results.

4 STUDY OBJECTIVES

This study aims to:

a. quantify the proportion of all babies admitted to neonatal units born to women with a hypertensive disorder of pregnancy
b. describe the national neonatal morbidity, mortality and resource use of babies admitted to neonatal units born to women with a hypertensive disorder of pregnancy
c. examine ethnic disparities in neonatal outcomes of babies admitted to neonatal units born to women with hypertensive disorders of pregnancy.

5 STUDY DESIGN

This study is a secondary analysis of an existing national electronic health record population cohort using anonymised, routinely recorded clinical data from the National Neonatal Research Database (NNRD). There will be no new patients recruited and there will be no changes made to patient care.

The NNRD is an approved research database constituting real-world prospective clinical data extracted from point-of-care neonatal electronic health records with complete coverage of infants admitted for neonatal care to National Health Service (NHS) neonatal units in England and Wales (since 2012) and Scotland (since 2015). A defined data extract of approximately 450 items (the Neonatal Data Set) is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London for data linkage and cleaning prior to entry into the NNRD. To date, the NNRD contains data for over a million babies (approximately 80,000 babies annually). High completeness and accuracy (>95%) of neonatal data held in the NNRD has been confirmed by formal comparison with a multicentre, randomised placebo-controlled trial.[15]

For study aims a-c, the research team will work with NNRD data analysts to extract anonymised data from the NNRD. A data dictionary and data extraction schema will be developed. The study cohort will comprise all babies admitted to and discharged from a neonatal unit in England and Wales between 2012 and 2020 inclusive. Extracted data items will include baby, maternal and paternal demographic characteristics (such as birthweight, gestational age at delivery, maternal and paternal age and ethnicity), antenatal and labour/delivery variables (such as medical complications prior to pregnancy, complications in current pregnancy, mode of delivery), and neonatal outcome and resource use data (such as survival to discharge, number of days of intensive care and diagnoses e.g. hypoglycaemia, necrotising enterocolitis). A full data extraction schema is available in the Appendix.

6 PARTICIPANT ENTRY CRITERIA

This study is a retrospective cohort study using anonymised data extracted from the NNRD. The cohort will comprise of babies admitted to and discharged from neonatal units in England & Wales between 2012 and 2020 inclusive (projected n≈ 575,000).

6.1 INCLUSION CRITERIA

The cohort will be extracted from the NNRD according to the following criteria:

- Babies admitted to and discharged from a neonatal unit between 2012 to 2020 inclusive.
- Received care in a neonatal unit in England and Wales (part of UK Neonatal Collaborative and therefore contributing data to the NNRD)
- All admission episodes

In addition we are requesting a separate data extraction for a subset of the cohort (babies admitted to two hospital sites: St Thomas' Hospital & King's College Hospital) to allow for comparison to local data at these sites available through the eLIXIR project.

6.2 EXCLUSION CRITERIA

There are no exclusion criteria.

7 OUTCOMES

7.1 RETROSPECTIVE COHORT STUDY

Outcomes have been chosen to align with the Neonatal Core Outcome Set where possible.[17] All outcomes will be defined as per standard Neonatal Data Analysis Unit (NDAU) operating procedures to allow comparability with other studies.

PRINCIPAL OUTCOMES

Neonatal - clinical

- Survival to discharge from neonatal care
- Primary recorded reason for neonatal unit admission

Neonatal – resource use

- Length of stay in neonatal unit
- Number of days of intensive care

SECONDARY OUTCOMES

Neonatal – clinical

- Survival to discharge from neonatal care without comorbidity
- Cause of death

- Age at death
- Discharge weight SDS (standard deviation score)
- Birthweight centile (z-score), birthweight SDS (standard deviation score).
- Clinical diagnoses:
    - Potentially specific to hypertensive disorder of pregnancy/antihypertensive agent treatment: fetal growth restriction/intrauterine growth restriction, hypoglycaemia,
    - General neonatal complications: Brain injury on imaging, necrotising enterocolitis, sepsis, jaundice, GI perforation.
    - Preterm complications: chronic lung disease/bronchopulmonary dysplasia, retinopathy of prematurity.

Neonatal – resource use

- Number of days of high-dependency care
- Number of days of special care
- Number of days of invasive respiratory support
- Number of days of non-invasive respiratory support
- Transfusion of blood product(s)
- Number of days of parenteral nutrition
- Method of feeding (number of days of each e.g. NG, breast etc)
- Number of days of types of feed e.g. IV dextrose, breastmilk, enteral etc.
- Number of days nil by mouth
- Number of days received any of mother's breastmilk
- Line type(s) (binary indicator variables for line types e.g. central line, umbilical venous catheter etc.)
- Surfactant administered
- Surfactant administered on first day

8 STATISTICAL AND DATA ANALYSIS PLAN

8.1 Determining the proportion of babies admitted to neonatal units born to women with a hypertensive disorder of pregnancy

The cohort of babies born to women with a hypertensive disorder of pregnancy (HDP) admitted to neonatal units in the extracted dataset (neonatal HDP cohort) will be defined according to the following NNRD variables:

- **Medical problems prior to pregnancy of mother:** Recorded history of chronic hypertension.
- **Obstetric problems during pregnancy:** One or more recorded diagnosis of any of: pre-eclampsia, severe pre-eclampsia, eclampsia, gestational hypertension/pregnancy-induced hypertension, HELLP (Haemolysis, elevated liver enzymes, low platelets) syndrome.
- **Medication given during labour:** Record of antihypertensive drug administration.

The number and proportion of all babies admitted to neonatal units in England and Wales born to women with a hypertensive disorder of pregnancy per annum over the study period will be reported according to gestational age categories.

8.2 Estimating neonatal morbidity, mortality and health resource use in babies admitted to neonatal units born to women with a hypertensive disorder of pregnancy

The background maternal and neonatal characteristics, birth and neonatal admission details, clinical

course, resource use and outcomes of the national neonatal HDP cohort will be described (see Outcomes Section 6.2). Results will be presented in aggregate and according to specific hypertensive disorder of pregnancy diagnoses (chronic hypertension, gestational hypertension, pre-eclampsia/ superimposed pre-eclampsia) and gestational age categories. Results will be presented as mean (standard deviation), medians (interquartile ranges) or count and proportions as appropriate. Temporal and geographical variation in principal neonatal outcomes for gestational age categories will be explored as described in previous studies utilising the NNRD.[18] In brief, temporal variation will be assessed by joinpoint regression to estimate time trends and geographical variation will be assessed by assigning infants to one of five regions (London, Midlands and East of England, North of England, South of England, Wales) on the basis of mothers' residence and comparing crude and standardised outcomes e.g. survival rate, across regions.

Comparison of the number of babies admitted to neonatal units in the NNRD cohort per annum (which will have complete national coverage of all neonatal unit admissions) with Office of National Statistics (ONS) annual birth statistics over the study period by gestational age will allow determination of the gestational age at birth cut-off at which we can be confident all live babies born were admitted to a neonatal unit (anticipated all babies born < 34 weeks gestation). For the subset of the study cohort born below this gestational age cut-off, we will be able to describe the national morbidity, mortality and resource use of *all* babies born to women with a hypertensive disorder of pregnancy at these gestational ages. In the remaining cohort, particularly babies born at term (> 37 weeks gestation), we will be describing the national outcomes of babies born to women with a hypertensive disorder of pregnancy for those infants which required admission to a neonatal unit, as no babies born to women with a hypertensive disorder of pregnancy who were not admitted to a neonatal unit will not be captured in the NNRD.

We will also be able to access maternal and baby denominator data for the babies admitted to St Thomas' Hospital and King's College Hospital (which will be extracted as a separate subcohort) as electronic health record data of all maternities are available through the KCL eLIXIR Dataset. This will allow further investigation of patterns of neonatal admission across all hypertensive women in this subset of the cohort.

Neonatal clinical outcomes and resource use (see Outcomes Section 6.2) in babies admitted to neonatal units exposed to a maternal hypertensive disorder of pregnancy in utero (neonatal HDP cohort) will be compared to babies not exposed to a maternal hypertensive disorder of pregnancy (remainder of neonatal cohort) using adjusted regression and survival analysis models. Informed by comparison to ONS data as described above, analysis will be restricted to babies born at the determined gestational age cut-off (anticipated < 34 weeks gestation) where all babies were admitted to neonatal units, with exploratory analysis of babies born at later gestational ages. Models will be adjusted for relevant maternal, delivery and fetal/pregnancy factors including maternal comorbidities, multifetal pregnancy, infant sex, gestational age, antenatal steroid administration, neonatal unit site and year of admission. Hypertensive disorder of pregnancy diagnosis will be inputted as a single aggregate label (any hypertensive diagnosis), and as separate labels (chronic hypertension, gestational hypertension, pre-eclampsia/ superimposed pre-eclampsia) in sensitivity analyses. An interaction test will be used to determine whether neonatal outcomes of maternal hypertensive disorder of pregnancy diagnosis are significantly modified by the presence/absence of fetal growth restriction (defined by birthweight z-score). If appropriate, mediation analysis will be used to further explore the hypothesis that adverse neonatal outcomes in babies admitted to

neonatal units born to women with a hypertensive disorder of pregnancy are mediated by fetal growth restriction.

8.3 Investigation of ethnic disparities in neonatal outcomes of babies born to women with hypertensive disorders of pregnancy admitted to neonatal units

The characteristics and outcomes of the neonatal HDP cohort as outlined in section 8.2 will additionally be described with stratification by maternal ethnicity (NHS England standard ethnic group codes). Comparison with Office of National Statistics (ONS) denominator data of livebirths according to maternal ethnicity by week of gestation (Birth characteristics dataset) over the study period will allow assessment of whether certain ethnic groups are over-represented in the neonatal HDP cohort.

Regression and survival analysis models developed in section 7.3 will be used to inform models including maternal ethnicity. Comparison of univariable models using maternal ethnicity alone and adjusted multivariable models (including appropriate maternal characteristics, delivery, and fetal factors) will enable investigation of any disparities observed in outcomes. Temporal and geographical variation over the study period will be assessed as described in section 8.2.

8.4 Missing data

Missing data is common in routine electronic health record datasets. Pattern of missingness will be explored and missing data assumptions investigated. Where missingness for a variable is low (< 5%), complete case analysis will be considered. Where missingness is between 5-40% missing data will be handled in sensitivity analyses using multiple imputation techniques where appropriate if MCAR/MAR assumptions are met. Where variables have high missingness (> 40%) the extent of the missing data will be reported and discussed as a limitation of the study and the variable will not be included in statistical models.

Maternal and baby ethnicity are key variables in this analysis (objective c). As imputation of ethnicity would be inappropriate, missing ethnicity data will be classed as a separate category with results reported for this group.

8.5 Sample size

We expect to extract anonymised data on approximately 575,000 admissions to neonatal units in England and Wales between 2012-2020 inclusive (based on an average of 72,000 neonatal unit admissions/annum). A small pilot study (unpublished) has suggested around 8.5% of neonatal unit admissions in the NNRD have a record of a maternal hypertensive disorder of pregnancy. This gives a projected sample size of around 49,000 for the neonatal HDP cohort. No relevant prior data exist to inform specific sample size calculations. However, in view of the large expected size of the neonatal HDP cohort, we anticipate being able to detect small effect sizes in analyses.

9 REGULATORY ISSUES

9.1 DATA FLOWS

i) Clevermed -> NNRD/Imperial (existing)

A defined data extract of approximately 450 items (the Neonatal Data Set) is transmitted quarterly from Clevermed to the Neonatal Data Analysis Unit at Imperial College London for data linkage and cleaning prior to entry into the NNRD.

ii) NNRD/Imperial -> Researchers/KCL (new)

For this study, existing anonymised (de-identified) data extracted from the NNRD will be transferred to study team researchers at KCL. A data sharing agreement for anonymised (de-identified) data only is being arranged for this purpose.

9.2 ETHICAL APPROVAL

Only existing anonymised data will be extracted from the NNRD for use in this study. The Neonatal Data Analysis Unit (NDAU) holds UK Research Ethics Committee approval, 21/LO/0024 (IRAS number 291589), and Confidential Advisory Group (CAG) approval, ECC 8-05(f/2010), to form the NNRD.

The study management group will request ethnical approval for this study (retrospective and validation study) from a Research Ethics Committee (REC) and appropriate Health Regulatory Authority. Following approval, the study management group will write to all neonatal units that contribute data to the NNRD with an overview of the study, a copy of the study protocol and REC approval. Individual units will be given the option of opting out from participation in the study. In such cases, data from their unit would be excluded in the data extraction for the project.

The study will be carried out in line with Good Clinical Practice (GCP) guidelines and the UK Policy Frame Work for Health and Social Care Research.

9.3 CONSENT

There is no participant recruitment in this study. Individual participant consent is not being requested.

9.4 SPONSOR AND INDEMNITY

Imperial College London is the sponsor of this study and holds the appropriate insurance policies.

9.5 FUNDING

This is an Academic Foundation Programme project requiring no salary funding. National Neonatal Research Database data extraction and data analyst support costs are being funded by the NIHR Research Professorship (Chappell).

9.6 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor of the study.

10 STUDY MANAGEMENT

This is a collaborative project between Imperial College London and King's College London. The Chief Investigator is based at the Neonatal Data Analysis unit, Chelsea and Westminster Hospital, Imperial College London. The Joint Chief Investigator, research students and statistician are based at The Department of Women and Children's Health, King's College London. The Neonatal Data Analysis Unit manages and hosts the National Neonatal Research Database with all necessary governance structures in place. The UK Neonatal Collaborative (all units in the UK) submit data with Caldicott Guardian approvals. A formal data sharing agreement is been arranged between Imperial College London and King's College London to allow transfer of anonymised study data.

The database to be used in this study is the NNRD; researchers, clinicians, managers, commissioners, and others are welcome and encouraged to utilise the NNRD. More details are available here: http://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

11 RESULTS DISSEMINATION

The results of this study will be published in peer-reviewed academic journals, presented at conferences and local meetings. A summary of the study will also be publicised on the NNRD website. The UK Neonatal Collaborative will be named collaborators and will be acknowledged in all academic publications.

The study team will also work with women with lived experience of high blood pressure in pregnancy from a range of ethnic backgrounds and relevant maternity groups and networks (e.g. national patient support charity Action on Pre-eclampsia) in order to achieve culturally sensitive interpretation and dissemination of results to pregnant women and lay audiences through media networks.

12 CONFIDENTIALITY

The Chief Investigator is registered under the Data Protection Act and will be responsible for adherence to Information Governance policies, General Data Protection Regulation (GDPR) and the UK Data Protection Act 2018 for this study, and will act as custodian of the data generated by the study.

13 REFERENCES

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14 APPENDICES

14.1 NNRD Data Extraction Schema

Purpose: Baseline, hypertensive disorder of pregnancy diagnosis & confounder variables	**NNRD data items to extract**
Baby demographic and birth information	- Anonymised unique baby identifier - Year and month of birth - Place of birth code - Birthweight - Phenotypic sex - Gestational age at birth* (weeks and days) - Ethnicity - Congenital abnormalities - Worst base deficit within 12 hours after birth (mmol/L) * the best obstetric estimate, initially based on last menstrual period and modified by antenatal ultrasound
Maternal demographic	- Year of birth (to derive age) - Postcode (to assign region) - Postcode LSOA - Qualification attainment level - Occupation - Ethnicity - Consanguinity of parents indicator
Paternal demographic	- Year of birth (to derive age) - Ethnicity
Antenatal variables	- Mother booked for/received antenatal care - Antenatal care site code - Mother's number of previous pregnancies (parity) - Fetus number total - Detailed anomaly scan - Fetal doppler studies - Medical problems prior to pregnancy of mother - Obstetric problems during pregnancy - Problems (Infectious or medical) during pregnancy - Haemoglobinopathology status - Smoking in pregnancy - Steroids given during pregnancy - Antenatal magnesium sulphate
Labour and delivery	- Meconium stained liquor - Medication given during labour - Mother's onset of labour - Anonymised date and time of rupture of membranes (number of minutes birth to event)

	- Maternal pyrexia in labour - Intrapartum antibiotics given - Presentation of foetus at delivery - Number of fetuses - Mode of delivery - Mothers labour status at time of caesarean - Spontaneous respiration time of onset - APGAR at 1/5/10 minutes - Methods of resuscitation - Drugs used during resuscitation - Admission: Cord artery pH - Admission: Cord venous pH - Admission: Cord artery pCO2 - Admission: Cord venous pCO2 - Admission: Cord lactate - Admission: Cord artery base excess - Admission: Cord venous base excess - Surfactant given during resuscitation
Purpose: Description of neonatal morbidity, mortality and resource use	**NNRD data items to extract**
Admission details	- Admission date and time anonymised (number of minutes birth to event) - Admission Year - Admission Month - Admitting neonatal unit site code - Episode of care - Location baby admitted from - Hospital baby admitted from location detail - Reason for admission (primary category of care required on admission) - Temperature at admission - Admission blood pressure - Admission heart rate - Respiratory rate at admission - Oxygen saturation at admission - Blood glucose concentration at admission - Clinical diagnoses on admission - Was Vitamin K permission given - Vitamin K indicator - Route of administration of Vitamin K
Diagnoses, daily data and discharge data	**Principal outcomes:** - Survival to discharge from neonatal care - Primary recorded reason for neonatal unit admission

	- Length of stay in neonatal unit - Number of days of intensive care **Secondary outcomes:** - Survival to discharge from neonatal care without comorbidity - Cause of death - Clinical diagnoses: intrauterine growth restriction/fetal growth restriction, hypoglycaemia, birthweight centile (z-score), brain injury on imaging, necrotising enterocolitis, sepsis, jaundice, chronic lung disease/bronchopulmonary dysplasia, retinopathy of prematurity - Number of days of high-dependency care - Number of days of special care - Number of days of invasive respiratory support - Number of days of non-invasive respiratory support - Number of days of parenteral nutrition **NNRD variables required for derivation of outcomes:** - Discharge date and time anonymized - Discharge destination - Discharge reason - Discharge destination ward - Date and time of death anonymized - Cause of death - If baby died was a post mortem done - If necrotizing enterocolitis diagnosed, did post mortem confirm this - Discharge: Oxygen therapy - Clinical diagnoses at discharge - Procedures performed And summaries of relevant daily data e.g. number of days of invasive respiratory support.