PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : CRESS UMR1153 – CENTRE DE RECHERCHE EN ÉPIDEMIOLOGIE ET STATISTIQUES
NOM DE L'EQUIPE : EAROH – ÉQUIPE DE RECHERCHE SUR LES ORIGINES PRECOCES DE LA SANTE
DIRECTEUR DE THESE : BARBARA HEUDE
ADRESSE : BATIMENT LERICHE, HOPITAL PAUL BROUSSE, 16 AVENUE PAUL-VAILLANT COUTURIER, 94807 VILLEJUIF

TITRE DE LA THÈSE : MATERNAL BLOOD PRESSURE TRAJECTORIES DURING PREGNANCY AND FETAL GROWTH: SOCIAL DETERMINANTS, CRITICAL WINDOWS, AND CLINICAL IMPLICATIONS

CO-ENCADRANT EVENTUEL : WEN LUN YUAN
EQUIPE DU CO-ENCADRANT : EAROH – ÉQUIPE DE RECHERCHE SUR LES ORIGINES PRECOCES DE LA SANTE
LABORATOIRE : CRESS UMR1153

PRESENTATION DU SUJET

Context

Globally, the incidence of hypertensive disorders of pregnancy (HDP) increased from 16 to 18 million, representing a total increase of about 11%, from 1990 to 2019.[1] HDP, which include chronic hypertension, gestational hypertension, and preeclampsia/eclampsia, are the leading cause of maternal and fetal morbidity and mortality in developed countries.[2] HDP are also important risk factors for long-term maternal cardiovascular disease and mortality.[3] Additionally, fetal intrauterine growth restriction (IUGR), induced by HDP, increases the offspring's risk of developing adverse cardiometabolic outcomes in later life.[4] In France, a recent large-scale study of pregnant women using data from the National Health Data System (SNDS) estimated an age-standardized HDP prevalence of 7.4% and observed an upward trend in HDP prevalence due to older age at first childbirth and the rising prevalence of obesity.[5]

Beyond the more proximal risk factors of HDP, socio-economic determinants rest undeniably at their systemic roots, as they do among many other adverse health outcomes. Reducing health inequalities during the "first 1,000 days" is a key part of global public health strategy to end preventable maternal and offspring deaths and promote the health and development of all children.[6] Evidence suggests that community-wide, or "ecological", socio-economic determinants could contribute to health inequalities independently of individual ones.[7,8] Socio-economic factors at both the individual and ecological level drive detrimental health behaviors such as unhealthy diet, smoking, and alcohol consumption. This is particularly relevant to study during pregnancy, as it is a period of high vulnerability for both mother and fetus. Understanding the interplay between individual- and community-level socio-economic factors on the risk of HDP is essential to strategic public health planning to prevent and tackle health inequalities during such a sensitive period.

In clinically-healthy pregnant women, BP falls gradually during the first trimester, reaching a nadir around 22–24 weeks, and rises again from 28 weeks, reaching preconception levels by 36 weeks of gestation.[9] As HDP are defined according to the maternal blood pressure levels after 20 gestational weeks, most previous studies have focused on the relationships between being "small-for-gestational age" (SGA) at birth and maternal blood pressure

levels during late pregnancy. Greater increases in mid-to-late pregnancy BP have indeed been shown to be associated with an increased risk of SGA at birth.[10] Evidence on the relationships between the blood pressure levels during early pregnancy and the risk of SGA at birth, however, are scarce and inconsistent.[10,11] Hence, the level of evidence on the existence of one or multiple critical windows of maternal blood pressure in relation to fetal growth needs to be reinforced.

Furthermore, current diagnostic criteria for gestational hypertension relies on BP thresholds in non-pregnant individuals. Recent literature suggests the existence of a continuum of risk of adverse birth outcomes in association with maternal BP at *all BP levels*, including those which do not meet the thresholds for hypertension.[11] Consequently, mothers not identified during the first prenatal visit using a single timepoint measure might still have a subclinical risk of adverse fetal and neonatal outcomes. Additionally, the application of one, non-specific threshold for the whole pregnancy period is controversial, given that maternal BP undergoes important changes throughout pregnancy due to physiological adaptations, as described above. Increasing evidence calls for the need to lower the diagnostic threshold for gestational hypertension.[12,13] The current body of research recommends additional studies to develop more evidence-based BP monitoring during pregnancy and further define its key determinants and critical periods, particularly considering the risk of IUGR.[14]

Objectives

In this context, this project will articulate around the following three specific objectives:

1. Investigate the associations between individual and contextual socio-economic indicators and blood pressure during pregnancy, and the mediating role of maternal lifestyle factors.
2. Identify critical windows of exposure of blood pressure variation during pregnancy in relation to fetal growth, as well as specific adverse, IUGR-related outcomes.
3. Evaluate the clinical implications of changing maternal blood pressure reference thresholds through the application of percentiles to achieve better sensitivity when diagnosing gestational hypertension, for better prevention of IUGR.

Methods

Study population

This project will rely on the analysis of data from the EDEN cohort, an ongoing French birth cohort study seeking to explore pre- and post-natal determinants of child health and development. Before their 24th week of amenorrhea, 2,002 women were enrolled from 2003 to 2006 in two mid-size cities, Nancy and Poitiers.

Variables of specific interest for this project

Up to 12 (Median (IQR) = 8 (6,9)) longitudinal measurements of BP throughout pregnancy were extracted from obstetric records, resulting in 1,875 mothers with available files including at least one BP measurement. Diagnoses of HDP, other pregnancy complications, chronic hypertension, relevant treatments and previous pregnancy medical history were also retrieved from these records. Preliminary analyses have derived internal, gestational age-specific BP z-scores using a Generalized Additive Model for Location, Scale and Shape (GAMLSS). This method allows modelling the whole distribution of a parameter (in our case, BP), which does not necessarily follow a proper gaussian distribution, against time (gestational age).[15]

Individual maternal socio-economic factors to be used in **axis 1** include education level, household income, marital status, and parity. At a contextual level, socio-economic factors were assessed from maternal residential addresses, such as the European Deprivation Index adapted to the French population. Other contextual community-level factors such as population density, building density, public transportation network density, facility density index and density of unhealthy food facilities are also available. Among pre-pregnancy maternal lifestyle factors, diet, alcohol consumption, and smoking behavior were collected, as well as BMI as a surrogate marker. A pre-pregnancy diet score, based on the "Dietary Approaches to Stop Hypertension" intervention, has also been previously derived.[16]

Fetal growth indices for **axis 2** were measured at routine fetal ultrasounds at 20-24- and 30-34-weeks' gestation and retrieved from obstetric records (N=1,833 and 1,752, respectively). Growth parameters included biparietal diameter, head circumference, abdominal circumference, and femur length. From these parameters, estimated fetal weight was derived using the Hadlock formula.[17] Uteroplacental blood flow was assessed through uterine and umbilical artery dopplers. Birthweight and placental weight were extracted from obstetric files and are available for 1,899 and 1,343 women, respectively. Customized birthweight z-scores (N=1,806) were derived adjusting for maternal height and weight, parity, fetal sex, and gestational age.[18] Infants with birthweight z-scores below the 10th percentile were classified as "small-for-gestational age".

Perinatal comorbidities of interest for **axis 3** will include preterm delivery (<37 weeks' gestation), small-for-gestational age, retroplacental hemorrhage, number of hospitalizations during pregnancy and infant admission to neonatal intensive unit care, all retrieved from obstetric records.

Statistical Analyses

In the case of missing covariates, either multiple or random forest imputation methods will be used for each axis, as applicable and necessary.

Axis 1: Linear mixture models, used to account for repeated BP data over time, will examine and dissect the roles of contextual and individual socio-economic factors to study the social gradient of BP trajectory during pregnancy. Mediation analyses will be conducted as a secondary step to investigate the potential mediating role of maternal pre-pregnancy multi-behavior patterns in this association.

Axis 2: The conditional standardized residuals model approach[19] will be applied to generate "conditional" BP, a residual of current BP at each timepoint, regressed on prior measurements. Conditional BP will represent the deviations from the expected evolution in BP from one gestational age to the next. We will then investigate the association between BP variations and fetal growth outcomes, in order to identify critical windows of exposure to elevated blood pressure during pregnancy. Birthweight to placental weight ratio, a proxy for placental efficiency, will also be considered as a secondary outcome of interest, among a smaller sub-sample of women with available data.

Axis 3: The analyses for this axis will use net reclassification indices[14] to calculate the improvements – or lack thereof – in the prediction of perinatal comorbidities, according to different classifications of hypertension based on maternal gestational-age specific percentiles of blood pressure. Beginning at the start of pregnancy, where a local maximum is observed in the sample's average BP, current (and lowered) diagnostic thresholds will be applied at each percentile and compared.

Number of subjects and study power

Proper power calculations cannot be applied to the statistical approaches proposed in this research project. However, we underline the fact that this project will rely on numerous (8 on average) repeated measurements of about 1900 women. This number of subjects would, for example, provide a power of more than 80% to detect a difference of 0.3 SD of BP Z-scores between mothers of babies born SGA or not.

Collaborations

The EAROH team is a partner of a European consortium studying environmental exposures and cardiometabolic health using harmonized cohort data (https://longitools.org/), permitting the potential replication of the first axis' analysis in other cohorts, and challenge the robustness of the observed estimates. One example is the ALSPAC British cohort, with 13,000 women with one or more blood pressure measurements during pregnancy.[11] Collaboration with international laboratories, including potential trimester(s) abroad, is therefore envisioned as a component of this doctoral project.

Provisional Calendar and Envisioned Articles

Articles	Tasks	S1	S2	S3	S4	S5	S6
Article 1 – Social inequalities in BP during pregnancy and the mediating role of lifestyle factors	Bibliography						
	Statistical analyses						
	Writing and submission of article						
	Revision						
Article 2 – Critical windows in BP variations for the risk of restricted fetal growth	Bibliography						
	Statistical Analyses						
	Writing and submission of article						
	Revision						
Article 3 – Should we adapt BP thresholds for a better detection of hypertensive disorders in pregnancy?	Bibliography						
	Statistical Analyses						
	Writing and submission of article						
	Revision						
Thesis Manuscript	Writing and sending to reviewers						

References

1. Wang W, Xie X, Yuan T, et al. Epidemiological trends of maternal hypertensive disorders of pregnancy at the global, regional, and national levels: a population-based study. *BMC Pregnancy Childbirth*. 2021;21(1):364.
2. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet Lond Engl*. 2006;367(9516):1066-1074
3. Tooher J, Thornton C, Makris A, et al. Hypertension in pregnancy and long-term cardiovascular mortality: a retrospective cohort study. *Am J Obstet Gynecol*. 2016;214(6):722.e1-6. doi:10.1016/j.ajog.2015.12.047
4. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359(1):61-73.
5. Olié V, Moutengou E, Grave C, et al. Prevalence of hypertensive disorders during pregnancy in France (2010-2018): The Nationwide CONCEPTION Study. *J Clin Hypertens Greenwich Conn*. 2021;23(7):1344-1353.
6. UNICEF Strategy for Health, 2016 - 2030 | UNICEF. Published August 1, 2016. Accessed May 21, 2023. https://www.unicef.org/reports/unicef-strategy-health-2016-2030
7. Feng X, Astell-Burt T. Neighborhood Socioeconomic Circumstances and the Co-Occurrence of Unhealthy Lifestyles: Evidence from 206,457 Australians in the 45 and Up Study. *PLOS ONE*. 2013;8(8):e72643.

8. Halonen JI, Kivimäki M, Pentti J, et al. Quantifying Neighbourhood Socioeconomic Effects in Clustering of Behaviour-Related Risk Factors: A Multilevel Analysis. *PLOS ONE*. 2012;7(3):e32937.
9. Ayala DE, Hermida RC, Mojón A, et al. Blood pressure variability during gestation in healthy and complicated pregnancies. *Hypertens Dallas Tex 1979*. 1997;30(3 Pt 2):611-618.
10. Bakker R, Steegers EAP, Hofman A, Jaddoe VWV. Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. *Am J Epidemiol*. 2011;174(7):797-806.
11. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Associations of Blood Pressure Change in Pregnancy with Fetal Growth and Gestational Age at Delivery: Findings from a Perspective Cohort. *Hypertension*. 2014;64(1):36-44.
12. Reddy M, Rolnik DL, Harris K, et al. Challenging the definition of hypertension in pregnancy: a retrospective cohort study. *Am J Obstet Gynecol*. 2020;222(6):606.e1-606.e21.
13. Sisti G, Fochesato C, Elkafrawi D, Marcus B, Schiattarella A. Is blood pressure 120-139/80-89 mmHg before 20 weeks a risk factor for hypertensive disorders of pregnancy? A meta-analysis. *Eur J Obstet Gynecol Reprod Biol*. 2023;284:66-75.
14. Bello NA, Zhou H, Cheetham TC, et al. Prevalence of Hypertension Among Pregnant Women When Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines and Association With Maternal and Fetal Outcomes. *JAMA Netw Open*. 2021;4(3):e213808.
15. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *J R Stat Soc Ser C Appl Stat*. 2005;54(3):507-554.
16. Aubert AM, Chen LW, Shivappa N, et al. Predictors of maternal dietary quality and dietary inflammation during pregnancy: An individual participant data meta-analysis of seven European cohorts from the ALPHABET consortium. *Clin Nutr Edinb Scotl*. 2022;41(9):1991-2002.
17. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements--a prospective study. *Am J Obstet Gynecol*. 1985;151(3):333-337.
18. Ego A, Subtil D, Grange G, et al. Customized versus population-based birth weight standards for identifying growth restricted infants: a French multicenter study. *Am J Obstet Gynecol*. 2006;194(4):1042-1049.
19. Zhang X, Tilling K, Martin RM, et al. Analysis of 'sensitive' periods of fetal and child growth. *Int J Epidemiol*. 2019;48(1):116-123.
20. Adair LS, Martorell R, Stein AD, et al. Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? *Am J Clin Nutr*. 2009;89(5):1383-1392.

PREREQUIS, FORMATION : MASTER EN SANTE PUBLIQUE / ÉPIDEMIOLOGIE / BIOSTATISTIQUES

CONTACT POUR CE SUJET : BARBARA HEUDE
EMAIL : BARBARA.HEUDE@INSERM.FR
TELEPHONE : +33 1 45 59 51 85

SPECIALITE DE LA THESE

Santé publique - Epidémiologie	☒
Santé publique - Epidémiologie clinique	☐
Santé publique - Epidémiologie sociale	☐
Santé publique - Epidémiologie génétique	☐
Santé publique - Biostatistique	☐
Santé publique - Biomathématiques	☐
Santé publique - Biostatistique et Biomathématiques	☐
Santé publique - Informatique médicale	☐
Santé publique - Imagerie biomédicale	☐

ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour l'Université Paris Cité : Isabelle Boutron

Santé publique - Bioinformatique ☐
Santé publique - Recherches sur les services de santé ☐
Santé publique - Economie de la santé ☐
Santé publique - Science des données ☐
Santé publique – Prévention et promotion de la santé ☐

SIGNATURE DU. DE LA DIRECTEUR.TRICE DE THESE

[redacted]

VISA DU.DE LA DIRECTEUR.TRICE DU LABORATOIRE
(DEROGATION DE SIGNATURE NON ACCEPTEE)

AVIS FAVORABLE ☑

[redacted]

Ecole Doctorale 393
Centre Biomédical des Cordeliers
15, rue de l'Ecole de Médecine 75006 Paris
https://ed393.sorbonne-universite.fr/

Contact : ed393@sorbonne-universite.fr/Téléphone : 01.44.27.24.35