PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : IPLESP - INSTITUT PIERRE LOUIS D’EPIDEMIOLOGIE ET DE SANTE PUBLIQUE

NOM DE L’EQUIPE : ERES- EQUIPE DE RECHERCHE EN EPIDEMIOLOGIE SOCIALE

DIRECTEUR DE THESE : GLADYS IBANEZ

ADRESSE : 27 RUE CHALIGNY, 75012, PARIS

TITRE DE LA THÈSE : MANAGEMENT OF ANTENATAL MATERNAL MOOD AND ANXIETY AND OFFSPRING DEVELOPMENTAL OUTCOMES

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EQUIPE DU CO-ENCADRANT : ERES

LABORATOIRE : U1136, IPLESP

PRESENTATION DU SUJET

Scientific context
Mood disorders are very common during the perinatal period, with major depression rates estimated at 12.4% and up to 25.0% for anxiety [1]. Antenatal mood disorders are associated with obstetric risks (e.g. preterm birth, low birth weight, intrauterine growth restriction) and short-term neonatal effects [2], but equally a broad range of offspring outcomes such as developmental difficulties, emotional and behavioral problems, and reduced cognitive performance [3]. Antidepressant or anxiolytic medications are therefore often considered necessary after weighing the known risks and benefits. In France, between 2.6% and 3% of pregnant women receive psychotropic drugs (SSRIs and SNRIs, benzodiazepines) for their mood disorder, of whom more than 50% start treatment during pregnancy [4,5]. However, large numbers of women stop taking medications when they discover they are pregnant, sometimes abruptly, because they are worried about harms to their baby.

Psychotropic medications are able to pass the placental barrier and may potentially influence fetal development. This is especially relevant during fetal life when the brain is vulnerable and various aspects of development may be impacted depending on timing of exposure during gestation [6]. Among newborns, prenatal psychotropic use (PPU) has been reported to increase risks for preterm and small for gestational age births, respiratory distress and certain congenital heart malformations [2]. Equally, PPU is associated with adverse short-term symptoms, including autonomic and motor activity and sleep [2,7]. While there is a substantial body of literature investigating effects on neonatal outcomes, studies of developmental outcomes later in childhood are limited. These studies generally report no or only small associations between early life psychotropic exposure and later language or cognitive problems [8], but the consequences on children’s behavioral and emotional development remain as yet insufficiently understood [9]. Recently, prenatal exposure (including the preconception period) to certain classes of SSRIs has been linked to autism spectrum disorder and ADHD [10], increased risk for internalizing problems [11] and reduced social behavior in early and middle childhood [6,8].

Further complicating our understanding of the mechanisms at play is the complex relationship between an unfavorable socioeconomic status (SES), mothers’ prenatal mood or anxiety and psychotropic use and child outcomes. It is well established that disadvantaged SES (low level of education, unemployment, low income) is associated with increased levels of child developmental problems [12]. Women at the lower end of the socioeconomic spectrum and with migrant status are also at increased risk for prenatal anxiety and depression [1]. Some studies have reported that disadvantaged women with a diagnosis of prenatal mood and anxiety problems were less likely to see a psychiatrist or specialist, and they were less likely to be medicinally treated than women in the highest income quintile [13]. Others, however indicated that they are more likely to use one or more psychotropic medication to manage mental illness during pregnancy than women of higher income [14]. Thus, the
finding that antidepressant use during pregnancy increases the risk of adverse offspring outcomes may actually be due to a relationship between social inequalities and adverse offspring outcomes.

Despite the high prevalence of depression and anxiety disorders in pregnant women, the impact of PPU on children's development, relative to untreated prenatal mood disorders is still insufficiently understood. In most epidemiological studies examining PPU the primary concern is confounding by indication [8]. This arises from the fact that individuals who are prescribed or who take a given medication may be inherently different from those who are not treated. One way to counter this is to include a contrast group of children exposed to depressive symptoms or anxiety, but whose mothers did not use psychotropic medication. Second, maternal mental health is often evaluated using self-completed questionnaires, which leads to information bias. Third, the low consideration of environmental risk factors such as the severity of mental health problems, co-prescriptions, prenatal smoking or alcohol use, prior history of depression and postnatal mental health and in particular socio-economic status, does not allow for the control of important confounders that might carry independent negative effects on children's development.

Objectives

Studying the complex relationships between maternal mood and anxiety disorders and the consumption of psychotropic substances during pregnancy with respect to the emotional reactivity of new-borns and their subsequent emotional, behavioral and cognitive development provides a better understanding of potential long-term vulnerability. Given the high prevalence of mood and anxiety disorders in women of childbearing age, promotion of optimal treatment during pregnancy is of major public health importance.

The first objective of this project is to examine the associations between mother's prenatal psychotropic drug use and children's adverse outcomes. The main child outcomes of interest are developmentally appropriate indices of emotional, behavioral and cognitive development (temperament, autistic symptoms, emotional difficulties, symptoms of hyperactivity and inattention, difficulties in language acquisition and general cognitive competence). The second objective is to characterize social inequalities in prenatal psychotropic use and assess in which extent they contribute to the association between antenatal maternal mood, psychotropic use and children's development.

Data

This project will rely on data from the ELFE cohort (French Longitudinal Study since childhood)[15]. This multidisciplinary cohort aims to describe children's health as well as their social and academic development up to the age of 20 and is nationally representative. The ELFE cohort recruited 18,321 children born in France in 2011 in 349 maternity wards. Information on psychological status and access to mental health care during pregnancy was collected by midwives during a face-to-face interview with the mothers in the maternity ward. Follow-up data is now available for 11,935 children being 3.5 years of age.

Maternal anxiety and depression will be measured as follows: (i) questionnaire data on persistent psychological difficulties during pregnancy (maternity), maternal depression at 2 months (EPDS) and at 12 months (SF12); Psychotropic drug use will be assessed through: (i) Self-reported psychotropic drug use during pregnancy; (ii) Information from the Systeme National d'Information Inter-régimes de l'Assurance Maladie (SNIIRAM) (national health insurance database). The SNIIRAM database consists of the anonymous and exhaustive recording of all reimbursements of patients' health expenditure, including drugs. Linkage of the ELFE cohort with participants' SNIIRAM data is currently ongoing and should be completed by the second trimester of 2019. Psychotropic drug use will be defined as at least one reimbursement during pregnancy according to the period of use (including the pre-conception period, i.e. the 90-day period preceding the estimated date of conception, and each pregnancy trimester). The detailed coding of the delivered drugs allows a precise view of the methods of care and the type of psychotropic prescribed to the mother.

Infant and Child developmental outcomes are assessed at different moments: Temperament (at 12 months), early autistic symptoms (M-CHAT at 2y), cognitive and psychomotor development (CDI at 2y and 3.5y), behavior (including symptoms of hyperactivity/inattention, SDQ from 3.5y).

Socioeconomic status: SES, as reflected by maternal educational level, employment during pregnancy, household gross yearly income and financial difficulties as well as migrant status will be studied as a predictor or potentially mediating factor of antenatal maternal mood, psychotropic use and children's development.
Methods
To test the hypotheses of the MAMMADO project, we will assign children to one of three groups: (i) children whose mothers reported psychotropic use during pregnancy (‘exposure’); (ii) children whose mothers reported having prenatal distress but no psychotropic use during pregnancy (‘untreated exposure’); and (iii) children whose mothers reported no prenatal depression or anxiety and no psychotropic use during pregnancy (‘unexposed’). To investigate the effects of the exposures of interest on child outcomes, we will first report unadjusted absolute risks and absolute risk differences. We will then calculate relative risks using conventional multivariable-adjusted regression methods. Additionally, a number of alternative statistical approaches will be used to strengthen causal inference and provide results that are more consistent with experimental evidence, including (i) Propensity scoring; and (ii) Negative control exposures to account for potential confounding.

Social inequalities in prenatal psychotropic use will be studied by univariate descriptive analysis and multivariate logistic regressions. The contribution of both prenatal and postnatal social inequalities in the association between antidepressant use during pregnancy and adverse offspring outcomes will be tested simultaneously in an analysis of causal pathways within a Structural Equation Modeling framework.

Planning
Month 1 – month 6: Literature review. First contact with the data, preparation of indicators for prenatal psychotropic use. First developments of statistical analysis.
Month 6 – month 12: Finalization and submission of paper I.
Month 13 – month 24: Analyses of socioeconomic status and PPU. Initial version of paper II submitted. Revision of paper I.
Month 25 – month 29: Revision of paper II. Preparation of the drafting of the thesis (detailed structure, additional bibliography, etc.).
Month 30 – month 33: Writing of thesis manuscript
Month 31 – month 36: Examination of the thesis by the defense committee members. Preparation of the defense. PhD defense

Topics of 2 articles
Paper I: The effects of PPU on children’s development compared to untreated maternal prenatal mood disorders and unexposed children
Paper II: The role of social inequalities in the associations between maternal antenatal mood, PPU, and child development

References


**PRÉREQUIS, FORMATION : MASTER DEGREE IN EPIDEMIOLOGY/BIOSTATISTICS/PUBLIC HEALTH**

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**SPECIALITE DE LA THESE**

- EPIDEMIOLOGIE (AVEC EVENTUELLEMENT MENTION CLINIQUE OU SOCIALE OU GENETIQUE)
- BIOSTATISTIQUE/BIOMETHEMATIQUES
- INFORMATIQUE MEDICALE (DONT IMAGERIE BIOMEDICALE, BIOINFORMATIQUE)
- RECHERCHES SUR LES SERVICES DE SANTE (DONT ANALYSE COUT EFFICACITE)

**VISA DU DIRECTEUR DU LABORATOIRE**

- AVIS FAVORABLE
- SIGNATURE

[Signature]