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SERENE: chronic Stress protection for postnatal dEpREssioN prEvention: an exploratory study

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SERENE: chronic Stress protection for postnatal dEpREssioN prEvention: an exploratory study

Tharwat Dahlia[1], Trousselard Marion[2], Balès Melanie[3], Sutter-Dallay Anne-Laure[3], Fromage Dominique[2], Spitz Elisabeth[4], Dallay Dominique[5], Harvey Thierry[1], Welter Eric[6], Coatleven Frédéric [5], Cherier Lydie[5], Teissedre Frédérique[7], Pouly Jean-Luc[8], Dutheil Frédéric[9], Duffaud Anaïs M.[2]

[1] Maternité GH Diaconesses Croix St Simon, F-75012 Paris, France

[2]Unité de Neurophysiologie du Stress, Département Neurosciences et Contraintes Opérationnelles, Institute de Recherche Biomédicale des Armées, F-91223 Brétigny-sur-Orge Cedex, France

[3] INSERM 1219, EPS Charles Perrens et Centre de Recherche, F-33000 Bordeaux, France

[4] University of Lorraine, Apemac, avenue de la Foret de Haye, F-54500 Vandœuvre-lès-Nancy, France

[5] CHU Pellegrin, University Hospital of Bordeaux, Centre Aliénor d'Aquitaine, F-33000 Bordeaux, France

[6] CHR Mercy, Regional Hospital of Metz, Pôle HFME, F-57000 Metz, France

[7] CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Department of In-Vitro Fecondation, Gynecologia, F-63000 Clermont-Ferrand, France

[8] Université Clermont Auvergne, UMR CNRS 6024, LaPSCo, Physiological and Psychosocial Stress, CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Occupational and Preventive Medicine, WittyFit, F-63000 Clermont-Ferrand, France

[9] Australian Catholic University, Faculty of Health, Melbourne, Victoria 3065, Australia

* Correspondences to: Anaïs Duffaud; anaisduffaud1@gmail.com

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Abstract

Introduction: The prevalence of postnatal depression (PND) is significant: up to 20% in a civilian setting. In mechanistic terms, the risk of PND lies in an interaction between a maternal psychophysiological vulnerability and a chronic environmental context of stress. On the one hand, stressor repetition during pregnancy mimics a chronic stress model that is relevant to the study of the allostatic load and the adaptive mechanisms. On the other hand, vulnerability factors reflect a psychological profile mirroring Mindfulness functioning (psychological quality that involves bringing one's complete and nonjudgmental attention to the present experience on a moment-to-moment basis).This psychological resource is linked to protective and resilient psychic functioning. Thus, PND appears to be a relevant model for studying the mechanisms of chronic stress and vulnerability to psychopathologies.

Methods and analysis: The study takes place in 4 maternities and will involve 260 women. We aim to determine the predictive psychobiological factors of PND emergence and to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We use a multidisciplinary approach that encompasses psychological resources and biophysiological and genetic profiles in order to detect relevant biomarkers for the vulnerability to face chronic stress and to develop PND. To do so, each woman will be involved in the study from her first trimester of pregnancy up to 9 months following delivery.

Ethics and dissemination: Ethics approval was obtained from the Ile de France III Ethics Committee, France (2016-A00887-44). We aim to disseminate the findings through international conferences and international peer-reviewed journals.

Trial registration: Clinical Trials identifier NCT03088319

Keywords: postnatal depression, stress, mindfulness, allostatic load

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Strengths and limitations of this study

- Multidisciplinary approach to postpartum depression: genetic, physiological and psychosocial with 2 time point peaks: 4 weeks and 6 months post-delivery.
- Identification of early-biomarkers that will be good predictors of postpartum depression in order to set up prophylactic intervention.
- Given the medical monitoring of none pathological pregnancies in France (mostly outside hospital until the last 2 months of pregnancy) we might struggle to include 260 participants in their first trimester.

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Background

Mounting evidence shows that the perinatal period is a time of increased vulnerability for mood disturbances and the onset of psychiatric disorders.[1, 2] Among puerperal disorders, baby blues, postnatal depression (PND) and puerperal psychosis are the most frequent [1]. While baby blues appears to be a normal adaptive phenomenon, PND and puerperal psychosis are psychopathologies associated with maternal suffering as well as having negative consequences on the offspring and family. PND, the most common complication of childbearing, has a prevalence range of 10 to 20% in western countries.[2, 3] It is described as a non-psychotic depressive episode of mild to moderate severity, beginning in or extending into the first postnatal year.[4] In the literature, two postpartum peaks have been identified: 4 weeks and 6 months post-delivery.[5, 6] It is also important to note that in 6 out of 10 women, PND is the first episode of depression.[7]

There is no specific diagnostic classification of PND. However, signs and symptoms are described in the DSM V as being similar to those observed in major depressive episodes but with a peripartum onset specifier (either before or after childbirth).[8-10] Therefore, the symptoms profile of PND is characterized by major negatives affects associated with anhedonia (loss of positive affect) and aboulia (behavioral disruption of sleep, appetite, etc.).[7] Such symptoms have to be observed for at least 2 weeks and to represent a change from previous functioning. PND has significant impact on the mother, her partner, the family, mother-infant interactions and on the long-term emotional and cognitive development of the baby. Besides the clinical diagnostic, the Edinburgh Postnatal Depression Scale (EPDS) is a screening tool widely used to detect and assess the severity of this pathology.[11]

During pregnancy and postpartum periods, the maternal organism undergoes remarkable biological, physical, social and emotional changes. The most studied biological mechanisms are neuroendocrine abnormalities. The hormone withdrawal hypothesis of PND is supported by a number of human and non-human studies: onset of depressive symptoms is linked to the sudden drop in the concentration of the ovarian hormones (estradiol and progesterone).[12, 13] Hypothalamo-pituitary-adrenal axis (HPA axis) dysfunction also seems to be implicated in PND onset. Corticotropin Releasing Hormone (CRH), Adreno Cortico Trophine Hormone (ACTH) and cortisol levels increase during pregnancy and up to a few days post-delivery and then normalize within 12 weeks post childbirth.[14, 15] Conversely, the involvement of thyroid function in the mother's major depressive episode remains unclear.[13]

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Recent neurobiological studies have provided evidence of the involvement of the emotional neuronal circuit in this psychopathology.[16, 17] GABA (γ-aminobutyric acid) is a potent neurotransmitter inhibitor that has been shown to be altered in PND,[18] mainly due to altered receptor functionality. It is worth noting that GABA functioning is highly dependent upon the oxidative status. Furthermore, three stress-modulator neurotransmitters seem to be directly or indirectly involved in PND: serotonin,[19] dopamine[20] and oxytocin. Chronic stress induces metabolic drift associated with reduced serotoninergic and dopaminergic transmission probably linked to inflammation as well as depression.[19] The deleterious effects of stressful situations during the postpartum period (up to 9 weeks) are buffered by endogenous oxytocin, thus protecting women from developing depression.[21]

Beyond its unique function during pregnancy, brain-derived neurotrophic factor (BDNF) is a key mediator in neuronal plasticity and in mental disorders such as depression.[22] The neurotrophin hypothesis argues that a stress-induced decrease of BDNF is linked with aberrant neurogenesis and subsequent major depression. This decreased BDNF activity in the brain is correlated with serum/plasma BDNF concentration. Low serum BDNF in late pregnancy is associated with higher depressive symptoms.[23]

Aside from hormonal and stress systems, immune dysregulation has also been hypothesized to contribute to PND. While pro-inflammatory cytokines decrease during pregnancy, anti-inflammatory cytokines increase. Within the first few hours after delivery, a sudden shift occurs leading to the installation of a pro-inflammatory state.[24] The role of the immune function in the pathophysiology of depression is now clear : higher levels of pro-inflammatory cytokines are associated with depressive episodes.[25]

Vulnerability to develop DPN also arises from genetic polymorphism.[26] Several lines of evidence suggest that (i) there is a specific genetic polymorphism of major depressive episodes occurring in the first year following birth and (ii) clinical severity of the depressive episode is linked to specific genetic variations.[27] Finally, epidemiological studies have shown an association between gene polymorphisms involved in stress regulation and mood disorders/PND.

Socio-economic and psychological factors are also of great importance in the risk of developing PND. Social context can be either protective (i.e. social support) or deleterious (i.e. low income), and thus responsible of stress levels during pregnancy.[28] Epidemiological studies show a link between maternal anxiety and mood symptoms during pregnancy and PND.[29] Personality aspects (such as neuroticism and low self-esteem)[30], as well as coping strategies[31], appear to be key factors in PND vulnerability.

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Mindfulness is a psychological quality that involves bringing one's complete attention to the present experience on a moment-to-moment basis and in a particular way: in the present moment, and nonjudgmentally.[32] This ability is associated with low neuroticism, high self-esteem and efficient coping.[33] In both healthy and sick people, mindfulness allows a better regulation of physiological and psychological stress.[34, 35] To the best of our knowledge, mindfulness and major maternal depressive episodes have never been studied. Since this ability is highly beneficial in preventing the development and relapse of depression,[36] one might expect PND to be less frequent in mindful women.

In light of the evidence gathered (biological, genetic and psychosocial), a hypothesis can be made: the risk of emergence of a PND relies on an interaction between a maternal psychobiological vulnerability and a chronic environmental context of stress. The PND appears as a relevant model for studying the mechanisms of chronic stress and vulnerability to psychological pathologies.

On the one hand, the repetition of stressors during pregnancy corresponds to a natural chronic stress model of several months and thus allows the study of the biological cost of responses to repeated stresses and the adaptive mechanisms leading to the functional drift to psychic dysfunction.

On the other hand, isolated vulnerability factors characterize a mirroring psychological profile of a Mindfulness type of functioning. This psychological resource has been associated with resistant or even resilient psychic functioning.

This study aims to follow a cohort of pregnant women from the first trimester of pregnancy to 6 months after delivery to determine the predictive psychobiological factors of the emergence of postnatal depression.

Objectives

The primary aim of the study is to determine the predictive psychobiological factors of the emergence of PND. It involves a multidisciplinary approach that will encompass psychological resources and biophysiological and genetic profiles.

The secondary aims are to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We will follow changes in biological, physiological and psychological parameters in order to detect relevant biomarkers of the vulnerability to face chronic stress and to develop PND.

Finally, two exploratory objectives will aim to assess the relevance of neurotrophic factors and genetic polymorphism in the risk of developing PND.

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Methods

Trial design and setting

We aim to undertake a multicentric prospective longitudinal study. The study will take place in hospitals where participants will be able to be included in their first trimester of pregnancy. So far, 4 hospitals will be involved: Pôle HFME, CHR Mercy, Metz - Maternité GH Diaconesses Croix St Simon, Paris - Centre Aliénor d'Aquitaine, CHU Pellegrin, Bordeaux and Unité FIV, Pôle gynécologie, obstétrique et reproduction, CHU Estaing**,** Clermont-Ferrand.

Eligibility criteria

The women involved in the study will have to meet the following requirements:

Inclusion criteria

- Before 14 weeks of gestation
- Pregnancy monitoring planned within one of the four facilities involved in the project
- Women over 18 years
- Covered by the French National Health Service

Non-inclusion criteria

- Pathological pregnancy requiring increased medical monitoring
- Multiple pregnancy
- Ongoing pathologies at the time of inclusion: (i) immune or endocrine conditions; (ii) any psychological disorders (PTSD, depression or anxiety disorders, etc.); or (iii) neurological pathologies such as multiple sclerosis.
- Hormonal or psychotropic drug therapies

End of the trial

During the study, if a participant meets one the following criteria, her participation will be discontinued:

- Withdrawal of consent
- Occurrence of a non-inclusion criteria
- Medical condition interfering with the protocol
- Death or « lost to follow-up »

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- If a pregnancy becomes "pathological", the participant will have the choice to continue or to stop her involvement in the project; the pathological event will be reported in the case report form.

The recruitment started in April 2017 and will last 12 months.

Adverse events and other unintended effects of the study will be reported in compliance with the code of the French public health.

Intervention – participant timeline

This study aims to follow pregnant women, civilian or military, from the first trimester of pregnancy up to 9 months post-birth. As shown in Figure 1, each woman will have to attend 10 visits: 1 visit during the first trimester (inclusion visit – VI); 1 visit every month during the others two trimesters of pregnancy (VP4 to VP9); 1 visit within the 48 hours after the birth (VB1); and 2 visits, 2 and 6 to 9 months after delivery (VB2 and VB3, respectively). The last two VB visits could be done at a distance. The follow-up includes genetic, biological, physiological and/or psychological parameters. During the inclusion visit, participants will have to go through the complete assessment: complete information on the protocol by competent person (medical doctor or midwife), signature of consent forms (one to participate in the study and one for the genetic analysis), psychological questionnaires, measurement of heart rate variability (HRV), genetic, hair and blood samplings. For the remaining 2 trimesters of pregnancy, psychological assessment and HRV measurement will be performed monthly whereas blood sampling will only be done on VP5 and VP8. Within 48 hours of the delivery (VB1), blood and hair will be collected and questionnaires will be filled. The last 2 visits (VB2 and VB3) will only require completing the psychological booklet. Details of the psychological questionnaires and genetics analyses can be found in tables 1 and 2.

Outcomes

The primary outcome of the study is the predictive psychobiological factors of the risk of developing PND. PND will be assessed using the Edinburgh Post Depression Scale - EPDS (with a screening cut off >11).[37] EPDS is a 10-item self-report questionnaire assessing symptoms of depression and anxiety. The factors assessed will encompass psychopathological and positive psychological aspects (see table 1 for detail of the questionnaires used).

The secondary outcomes will contribute to understand the mechanisms involved in stress throughout the pregnancy:

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(i) Biological stress: GABA, TBARS (thiobarbituric acid reactive substances), inflammatory cytokines and endobiogenic index.

(ii) Physiological stress: activation of the autonomous nervous system through the measurement of heart rate variability (HRV).

(iii) Psychological stress: perceived stress, social support and life quality.

The exploratory objectives will include the study of genetic polymorphisms linked to stress vulnerability (see table 2) and central functioning (BDNF and 8 iso-prostaglandine F2a).

Material

Heart Rate Variability: HRV will be sampled in order to assess the reactivity of the autonomic nervous system (ANS). HRV will be recorded on a monthly basis using the CODESNA Physioner system. Heart rate, HRV components (high frequency, HF; low frequency, LF, and LF/HF ratio) will be examined as described by the Task Force.[38]

Questionnaires: The psychological assessment will encompass pathological, personality, and positive psychology aspects. All the questionnaires chosen are self-reported questionnaires that have been validated in French and have demonstrated good psychometric properties. Ideally, all these assessments should be performed before any potential stressful exam.

Blood, hair and genetic samplings: All sampling will be conducted according to the standard operating procedures described by the promotor and in accordance with the local procedures. Hair, blood and genetic samples will be conditioned locally and stored at room temperature or -20°C. All the biological materiel will be then transferred for analyses to laboratories (Biolabs or IRBA) by a professional delivery company.

Statistics

Number of participants needed

Several lines of evidence have been used in order to determine the number of participant require.

1/ Maternity activities: over 2 500 births/year in CHU Pellegrin and CHR Mercy, 1 000 births/year in GH Diaconesses Croix St Simon and up to 200 medically-assisted procreations in the CHU Estaing.

2/ In the general population, PND prevalence is 20%, therefore if we include 260 subjects, 52 should be diagnosed with PND. Among these, 5% of the mothers-to-be might discontinue the SERENE project before completion, so 42 participants with PND should remain.

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3/ Psychometric tools used in the general population show that it is possible to distinguish between mindful and less mindful subjects within a sample of 20 subjects (Friburg Mindful Inventory cut-off score above 37). However, since mindfulness has never been assessed in pregnant women, no threshold between high and low mindfulness has been determined in such a population.

4/ Given the figure for stress in the general population (30%), we expect to get 78 stressed subjects among the 260 participants included.

Therefore, we aim to recruit 260 participants, which represents less than 5% of total pregnancies followed up in the 4 centers in one year.

General design

Central tendency and the variability of the continuous variables will be described depending on whether or not they follow a normal distribution (using the Shapiro-Wilk test) : if there is normal distribution, data will be summarized using means and standard deviations, if not medians and ranges will be used. VAS variables will be analyzed like ordinal data and described as previously.

If require, class gathering into categorical variables will be performed. These variables will be described as absolute values and percentages.

Any variable with more than 10% missing data will not be analyzed.

Analyses for the primary outcome

A cut-off score of 11 in EPDS has been shown to be a sensitive and specific threshold of PND emergence. We will use multivariate logistic regression in order to detect predictive factors of PND emergence. Threshold sensitivity in terms of sensitivity, specificity and predictive value will be done using Receiver Operating Characteristic (ROC) analysis.

A two-step approach will be conducted. Firstly, a theme reasoned mixed approach will be undertaken to evaluate the weight of each biomarker for PND risk. 4 themes have been identified: (i) biography (full-term delivery, life events), (ii) psychological resources, (iii) biophysiological profiles and (iv) genetic. A final model will then be determined using mixed logistic regression from variables that will have been selected from the previous step.

Analyses for the secondary and exploratory outcomes

The role of each biomarker and psychological factor in PND will be compared between the 2 groups (PND and non-PND) using an ANOVA factorial analysis. Life events during the

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pregnancy and status (civilian, military or spouse of force personnel) will be considered. Risk factors of PND linked to difficult labour/delivery will be controlled.

Finally, a composite index taking all the relevant biomarkers together will be computed in order to have a single predictive variable for the risk of developing PND.

Data collection and management

In each centre involved in the SERENE project, an assistant will be in charge of conducting the project according to the protocol in order to ensure the quality of the data collected and to promote participant retention. Implementation and conduct of the study will be done by the CRA coordinator of the DCSSA according to the monitoring plan. As much as possible, she/he will ensure the quality of data collection in each center in order to minimize missing data.

Personal information, Data entry, coding, security and storage are processed in compliance with the Act of 6 January 1978 on Data Processing, Data Files and Individual Liberties.

Ethics and dissemination

Ethical approval has been obtained from the Ile de France III Ethics Committee (Hopital Tarnier-Cochin, Paris), France (2016-A00887-44). The study poses little to no risk to the participants or their infants, and does not interfere with the typical care received during pregnancy. This protocol will certainly detect some episodes of depression; such an event will be communicated to the caregivers or the participant herself in order to set up an adequate alternative care. Study results will be disseminated at national and international conferences and in peer-reviewed journals. The trial findings could also be made available to participants collectively. Every protocol modifications will be submitted to competent authorities (if required) and communicated to every relevant parties according to the code of the French public health.

All the data will remain the sponsor property. The final data report will be written out by all the associated scientific investigators (as defined in the protocol).

Discussion

Potential limitations

We have identified two potentials limitations:

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(i) Given the medical monitoring of none pathological pregnancies in France (mostly outside of hospitals until the last 2 months of pregnancy) we might struggle to include 260 participants in their first trimester. This is why we made sure to set up a "recruiting network" (i.e. involvement of doctors doing first trimester ultrasounds, network of independent midwives) in each maternity, which should help to reach this goal.

(ii) For the study, participants need to attend 10 visits, which might seem demanding. Furthermore, the last two visits are of importance since it is during these that PND might be diagnosed. So, to make sure that participants will complete the protocol, one person (other than the investigators) is in charge of the participants' follow-up in each maternity.

Trial status

The study is currently recruiting participants.

Abbreviations

ANS : Autonomic Nervous System

ACTH**:** Adreno Cortico Trophine Hormone

BDNF: brain-derived neurotrophic factor

CRH: Corticotropin Releasing Hormone

EPDS: Edinburgh Postnatal Depression Scale

GABA: γ-aminobutyric acid

HPA axis: Hypothalamo-Pituitary-Adrenal axis

HRV: Heart Rate Variability

PND: PostNatal Depression

PTSD: Post Traumatic Stress Disorder

TBARS: Thiobarbituric Acid Reactive Substances

Contributors

Trousselard M, Tharwat D, and Duffaud A were involved in the conception and trial design. They also wrote the draft of the article. Sutter-Dallay A, Dallay D, Spitz E, Harvey T, Welter E, Pouly JL and Dutheil F contributed to the refinement of the study protocol and provided expert insight. Trousselard M, Fromage D, Duffaud A were responsible for the ethics committee. All the authors were involved in final approval of the manuscript.

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The SERENE project is founded by the French Defence Procurement Agency (DGA).

Roles and responsibilities

The study sponsor is the Direction centrale du service de santé des armées (DCSSA - Fort neuf de Vincennes, Cours des maréchaux, 75 614 Paris Cedex 12). The coordinator, clinical research associate coordinator and the "Bureau de gestion de la recherche Clinique" are in charge of the study logistics: quality of the collected data in the CRF, creation of input masks, computerization and quality control of data. Since the study does not involve the use of product or medication and only represents minor risks and constrains, no data monitoring committee has been called.

Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Since the manuscript is a protocol paper there is no unpublished data. The original protocol (version 2 – 25.07.2016) for this study is available by contacting the corresponding author via email.

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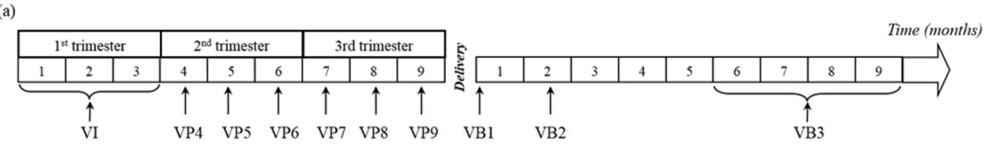
(a)



(b)

	PREGNANCY							POST-BIRTH		
	Inclusion visit = first trimester visit VI	Monthly visit during trimester 2 and 3						Follow-up visit post delivery		
		VP4	VP5	VP6	VP7	VP8	VP9	VB1	VB2	VB3
Notice – Consent form	x									
Genetic sampling	x									
Heart Rate Variability	x	x	x	x	x	x	x			
Blood sampling	*x*		*x*			*x*		*x*		
Hair sampling	*x*							*x*		
Questionnaires booklet	x	x	x	x	x	x	x	x	x	x

Figure 1 : Synopsis of study design. (a) Study timeline for each participant and (b) Details of visit requirements. Each participant will have to attend 10 visits from their 1st trimester of pregnancy up to 9 months post-delivery. VI: inclusion visit; VP4 to VP9: one visit every month during the last two trimesters of pregnancy; VB1: one visit within the 48 hours after delivery/birth; VB2: one visit 2 months after delivery/birth; VB3: one visit 6 to 9 months after delivery/birth.

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		PREGNANCY		POST BIRTH	
		Inclusion visit	VG4 to VG9	VP1	VP2 & VP 3
Pathological	Symptom Checklist 90	x			
	State-Trait Anxiety Inventory	x		x (state)	x (state)
	Edinburg Postnatal Depression Scale	x		x	x
	PTSD Checklist for DMS-5	x			x
	Profile of Mood Scale	x	x		
	Traumatic Event Scale			x	
	Peritraumatic Dissociative Experiences Questionnaire			x	
	Traumatic Delivery Impact			x	
	Maternal Self Esteem				x
Personality	Temperament and Character Inventory	x			
Positive Psychology	Freiburg Mindfulness Inventory	x			
	Warwick Edinburg Mental Well-Being Scale	x			
	Prenatal Antenatal Inventory	x	x		
	Multidimensional Scale of Perceived Social Support	x	x	x	x
	Labour Agentry Scale			x	
Visual Analogic Scale	Professional stress	x	x		
	Personal stress	x	x		
	Sleep; Quality	x	x		
	Delivery Anticipatory Stress	x	x		
	Medical staff support			x	

Table 1: Summary of psychological and psychopathological questionnaires.
VP4 to VP9: one visit every month during the last two trimesters of pregnancy; VB1: one visit within the 48 hours after delivery/birth; VB2: one visit 2 months after delivery/birth; VB3: one visit 6 to 9 months after delivery/birth.

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Genes		Function
BDNF	Brain-Derived Neurotrophic Factor	Neuronal growth factor linked to the development of psychopathologies (such as anxiety)
COMT	Catechol-O-Methyltransferase	Involved in stress regulation (catecholamine)
NPY	Neuropeptide Y	Role in stress response, circadian rhythms and cardiovascular functions
NR3C1	Glucocorticoid Receptor (GR)	GR transcription factor
NR3C2	Mineralocorticoid Receptor (MR)	MR transcription factor
FKBP5	FK506 Binding Protein 5	Gene encoding co-chaperone protein essential in GR signalling
SLC6A4	Sodium-Dependent Serotonin Transporter	Serotonin transporter gene
NPS	Neuropeptide S	Involved in anxiety, hyperactivity, food intake and sleep duration
NPSR1	Neuropeptide S Receptor	
CRHR1	Corticotropin Releasing Hormone Receptor	Involved in HPA axis regulation
DRD2	Dopamine Receptor D2	G protein-coupled receptor
OXT	Oxytocin/Neurophysin I Prepropeptide	Role in cognition, maternal behavior and cardiovascular functions
HMNCN1	Hemicentin-1	Protein involved in postpartum depression

Table 2 : Summary of gene polymorphism analysis
The single-nucleotide polymorphisms chosen aim to characterize vulnerability and severity of postnatal depression as well as stress sensitivity.

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RECUEIL de CONSENTEMENT

FACTEURS DE PROTECTION DU STRESS CHRONIQUE : ETUDE EXPLORATOIRE APPLIQUEE A LA DEPRESSION POST-NATALE (DPN)

Je soussignée (Nom, Prénom) .....

Née le ..... et demeurant à .....

.....

déclare avoir pris connaissance des informations orales et écrites qui m'ont été données concernant la recherche biomédicale « Facteurs de protection du Stress chronique : étude exploratoire appliquée à la dépression post-natale » - Projet SEREINE : StrEss dépREssion mINdfulnEss

J'ai reçu de l'investigateur toutes les informations nécessaires concernant l'objectif de cette recherche, son déroulement ainsi que de mes conditions de participation, de mes droits, des bénéfices attendus, des contraintes et des risques prévisibles.

J'ai pu poser toutes les questions que je voulais et j'ai reçu les réponses adaptées. De plus, j'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement. J'ai également compris que je pouvais refuser de participer à cette étude sans que cela ne porte préjudice à la suite de ma prise en charge.

J'accepte donc librement et volontairement de participer à cette recherche biomédicale.

☐ **J'accepte / ☐ je refuse que mes échantillons de cheveux et de sang prélevés dans le cadre de cette étude soient conservés et stockés à l'IRBA et au laboratoire de la maternité après avoir été codés.**

Ce consentement ne décharge ni l'investigateur, ni le promoteur de leurs responsabilités à mon égard. Je suis consciente que mes droits ne seront en aucune manière affectés par la signature de ce consentement. Je pourrais à tout moment retirer mon consentement, sans justification et sans conséquence pour la qualité des soins qui me seront donnés ou pour ma relation avec mon médecin.

J'ai été informée que pour la réalisation de cette recherche, le Comité de Protection des Personnes (CPP) Ile de France III a rendu un avis favorable le 21/06/2016 et que l'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) a donné son autorisation le 05/08/2016. J'ai également pris connaissance que le Promoteur, la Direction Centrale du Service de Santé des Armées, est son propre assureur et a autorisé cette étude.

J'ai noté que les données recueillies lors de cette recherche demeureraient strictement confidentielles et pourraient être consultées si j'en fais la demande. J'ai été informée que ces données pourront être consultées par l'investigateur, ses collaborateurs, des personnes mandatées par le promoteur et astreintes au secret professionnel et par des personnes mandatées par les autorités sanitaires. J'accepte également le traitement informatisé des données en conformité avec les dispositions de la loi relative à l'informatique, aux fichiers et aux libertés et j'ai pris connaissance de mon droit d'accès et de rectification.

Pour finir, je certifie être affiliée ou bénéficier d'un régime de sécurité sociale.

Partie à remplir par le patient	
Date :	**Signature :**

Partie à remplir par l'investigateur	
Nom et prénom :	
Date :	**Signature :**

En trois exemplaires originaux : l'un qui doit être gardé 15 ans pour l'investigateur, un second pour la patiente, un troisième pour le promoteur.

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RECUEIL de CONSENTEMENT GENETIQUE

FACTEURS DE PROTECTION DU STRESS CHRONIQUE : ETUDE EXPLORATOIRE APPLIQUEE A LA DEPRESSION POST-NATALE (DPN)

Je soussignée (Nom, Prénom) .....

Née le ..... et demeurant à .....

.....

déclare avoir pris connaissance des informations orales et écrites qui m'ont été données concernant la recherche biomédicale « Facteurs de protection du Stress chronique : étude exploratoire appliquée à la dépression post-natale » - Projet SEREINE : StrEss dépREssion mINdfulnEss

J'ai reçu de l'investigateur toutes les informations nécessaires concernant l'objectif de cette recherche, son déroulement ainsi que de mes conditions de participation, de mes droits, des bénéfices attendus, des contraintes et des risques prévisibles.

J'ai pu poser toutes les questions que je voulais et j'ai reçu les réponses adaptées. De plus, j'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement. J'ai également compris que je pouvais refuser de participer à cette étude sans que cela ne porte préjudice à la suite de ma prise en charge.

J'accepte donc librement et volontairement de participer à cette recherche biomédicale.

☐ **J'accepte / ☐ je refuse que la goutte de sang prélevée dans le cadre de cette étude soit conservée et stockée à l'IRBA après avoir été codée en vue d'analyses génétiques strictement décrites dans le protocole.**

Ce consentement ne décharge ni l'investigateur, ni le promoteur de leurs responsabilités à mon égard. Je suis consciente que mes droits ne seront en aucune manière affectés par la signature de ce consentement. Je pourrais à tout moment retirer mon consentement, sans justification et sans conséquence pour la qualité des soins qui me seront donnés ou pour ma relation avec mon médecin.

J'ai été informée que pour la réalisation de cette recherche, le Comité de Protection des Personnes (CPP) Ile de France III a rendu un avis le 21/06/2016 et que l'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) a donné son autorisation le 05/08/2016. J'ai également pris connaissance que le Promoteur, la Direction Centrale du Service de Santé des Armées, est son propre assureur et a autorisé cette étude.

J'ai noté que les données recueillies lors de cette recherche demeureraient strictement confidentielles et pourraient être consultées si j'en fais la demande. J'ai été informée que ces données pourront être consultées par l'investigateur, ses collaborateurs, des personnes mandatées par le promoteur et astreintes au secret professionnel et par des personnes mandatées par les autorités sanitaires. J'accepte également le traitement informatisé des données en conformité avec les dispositions de la loi relative à l'informatique, aux fichiers et aux libertés et j'ai pris connaissance de mon droit d'accès et de rectification.

Pour finir, je certifie être affiliée ou bénéficier d'un régime de sécurité sociale.

Partie à remplir par le patient	
Date :	**Signature :**

Partie à remplir par l'investigateur	
Nom et prénom :	
Date :	**Signature :**

En trois exemplaires originaux : l'un qui doit être gardé 15 ans pour l'investigateur, un second pour la patiente, un troisième pour le promoteur.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 12
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____4 onwards
	6b	Explanation for choice of comparators	_____NA_____
Objectives	7	Specific objectives or hypotheses	_____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____ 9 & 11___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8 & Figure 1__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____11_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____NA_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____NA_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____NA_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____11_____

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files 1 & 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Chronic Stress protection for postnatal dEpREssioN prEvention (SERENE): an exploratory study

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Complementary medicine
Keywords:	postnatal depression,, stress, mindfulness, allostatic load

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Manuscripts

Chronic Stress protection for postnatal dEpREssioN prevention (SERENE): an exploratory study

Tharwat Dahlia[1], Trousselard Marion[2], Balès Melanie[3], Sutter-Dallay Anne-Laure[3], Fromage Dominique[2], Spitz Elisabeth[4], Dallay Dominique[5], Harvey Thierry[1], Welter Eric[6], Coatleven Frédéric [5], Cherier Lydie[5], Teissedre Frédérique[7], Pouly Jean-Luc[8], Dutheil Frédéric[9], Duffaud Anaïs M.[2]

[1] Maternité GH Diaconesses Croix St Simon, F-75012 Paris, France

[2]Unité de Neurophysiologie du Stress, Département Neurosciences et Contraintes Opérationnelles, Institute de Recherche Biomédicale des Armées, F-91223 Brétigny-sur-Orge Cedex, France

[3] INSERM 1219, EPS Charles Perrens et Centre de Recherche, F-33000 Bordeaux, France

[4] University of Lorraine, Apemac, avenue de la Foret de Haye, F-54500 Vandœuvre-lès-Nancy, France

[5] CHU Pellegrin, University Hospital of Bordeaux, Centre Aliénor d'Aquitaine, F-33000 Bordeaux, France

[6] CHR Mercy, Regional Hospital of Metz, Pôle HFME, F-57000 Metz, France

[7] CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Department of In-Vitro Fecondation, Gynecologia, F-63000 Clermont-Ferrand, France

[8] Université Clermont Auvergne, UMR CNRS 6024, LaPSCo, Physiological and Psychosocial Stress, CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Occupational and Preventive Medicine, WittyFit, F-63000 Clermont-Ferrand, France

[9] Australian Catholic University, Faculty of Health, Melbourne, Victoria 3065, Australia

* Correspondences to: Anaïs Duffaud; anaisduffaud1@gmail.com

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Abstract

Introduction: The prevalence of postnatal depression (PND) is significant: reaching up to 20% in a the general population. In mechanistic terms, the risk of PND lies in an interaction between a maternal psychophysiological vulnerability and a chronic environmental context of stress. On the one hand, repetition of stressor during pregnancy mimics a chronic stress model that is relevant to the study of the allostatic load and the adaptive mechanisms. On the other hand, vulnerability factors reflect a psychological profile mirroring Mindfulness functioning (psychological quality that involves bringing one's complete and nonjudgmental attention to the present experience on a moment-to-moment basis). This psychological resource is linked to protective and resilient psychic functioning. Thus, PND appears to be a relevant model for studying the mechanisms of chronic stress and vulnerability to psychopathologies.

In this article, we present the protocol of an ongoing study (started in May 2017).

Methods and analysis: The study is being carried out in 5 maternities and will involve 260 women. We aim to determine the predictive psychobiological factors for PND emergence and to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We use a multidisciplinary approach that encompasses psychological resources and biophysiological and genetic profiles in order to detect relevant vulnerability biomarkers for chronic stress and the development of PND. To do so, each woman will be involved in the study from her first trimester of pregnancy until 12 months post-delivery.

Ethics and dissemination: Ethics approval was obtained from the Ile de France III Ethics Committee, France (2016-A00887-44). We aim to disseminate the findings through international conferences and international peer-reviewed journals.

Trial registration: Clinical Trials identifier NCT03088319

Keywords: postnatal depression, stress, mindfulness, allostatic load

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Strengths and limitations of this study

- Multidisciplinary approach to postpartum depression: genetic, physiological and psychosocial with 3 time points: 1, 6 and 12 months post-delivery.
- Identification of early-biomarkers that will be good predictors of postpartum depression in order to set up prophylactic intervention.
- Given the way none pathological pregnancies are medically monitored in France (mostly outside of hospitals until the last 2 months of pregnancy) it may be difficult to include 260 participants in their first trimester.

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Background

Mounting evidence shows that the perinatal period is a time of increased vulnerability for mood disturbances and the onset of psychiatric disorders [1, 2]. Among puerperal disorders, baby blues, postnatal depression (PND) and puerperal psychosis are the most frequent [1]. While baby blues appears to be a normal adaptive phenomenon, PND and puerperal psychosis are psychopathologies associated with maternal suffering and have negative consequences for the offspring and the family. PND, the most common childbearing complication, has a prevalence range of 10 to 20% in western countries [2, 3]. It is described as a non-psychotic depressive episode of mild to moderate severity, beginning in or extending into the first postnatal year [4]. In the literature, two postpartum peaks have been identified: 4 weeks and 6 months post-delivery [5, 6]. It is also important to note that PND is the first episode of depression in 6 out of 10 women [7].

There is no specific diagnostic classification of PND. However, signs and symptoms are described in the DSM V as being similar to those observed in major depressive episodes but with a peripartum onset specifier (either before or after childbirth) [8-10]. Therefore, the symptoms profile of PND is characterized by major negative effects that are associated with anhedonia (loss of interest in pleasurable activities) and aboulia (e.g. behavioral disruption of sleep, appetite, etc.) [7]. Such symptoms have to be observed for a minimum of 2 weeks and must represent a change from the previous functioning. PND has significant impact on the mother, her partner, the family, mother-infant interactions and on the long-term emotional and cognitive development of the baby. Besides being used for clinical diagnosis, the Edinburgh Postnatal Depression Scale (EPDS) is a screening tool widely used to detect and assess the severity of the depression [11].

During pregnancy and postpartum periods, the maternal organism undergoes remarkable biological, physical, social and emotional changes. The most studied biological mechanisms are neuroendocrine abnormalities. The hormone withdrawal hypothesis of PND is supported by a number of human and non-human studies: the onset of depressive symptoms is linked to the sudden drop in the concentration of ovarian hormones (estradiol and progesterone) [12, 13]. Hypothalamo-pituitary-adrenal axis (HPA axis) dysfunction also seems to be implicated in PND onset. Corticotropin Releasing Hormone (CRH), Adreno Cortico Trophine Hormone (ACTH) and cortisol levels increase during pregnancy and up to a few days post-delivery and then normalize within 12 weeks post childbirth [14, 15]. Conversely, the involvement of thyroid function in the mother's major depressive episode remains unclear [13].

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Recent neurobiological studies have provided evidence for the involvement of the emotional neuronal circuit in this psychopathology [16, 17]. GABA (γ-aminobutyric acid) is a potent inhibitory neurotransmitter that has been shown to be altered in PND (decreased inhibition), mainly due to altered receptor functionality [18]. It is worth noting that GABA functioning is highly dependent upon the oxidative status, which is a consequence of an imbalance between the production of free radicals and the failure of the antioxidant defense mechanisms. This dysregulation has been observed in psychopathological disorders such a depression [19].

Furthermore, three stress-modulator neurotransmitters seem to be directly or indirectly involved in PND: serotonin, dopamine and oxytocin [20][21]. Chronic stress induces metabolic drift associated with reduced serotoninergic and dopaminergic transmission, and is probably linked to inflammation as well as depression [20]. The deleterious effects of stressful situations during the postpartum period (up to 9 weeks) are buffered by endogenous oxytocin, thus protecting women from developing depression [22].

Other than its unique function during pregnancy, brain-derived neurotrophic factor (BDNF) is a key mediator in neuronal plasticity and in mental disorders such as depression [23]. The neurotrophin hypothesis argues that a stress-induced decrease of BDNF is linked with aberrant neurogenesis and subsequent major depression. This decreased BDNF activity in the brain is correlated with serum/plasma BDNF concentration. Low serum BDNF in late pregnancy is associated with higher depressive symptoms [24].

In addition to hormonal and stress systems, immune dysregulation has also been hypothesized to contribute to PND. While pro-inflammatory cytokines decrease during pregnancy, anti-inflammatory cytokines increase. Within the first few hours after delivery, a sudden shift occurs that leads to the installation of a pro-inflammatory state [25]. The role of the immune function in the pathophysiology of depression is now clear : higher levels of pro-inflammatory cytokines are associated with depressive episodes [26].

Vulnerability to develop PND also arises from genetic polymorphism [27]. Several lines of evidence suggest that (i) there is a specific genetic polymorphism of major depressive episodes occurring in the first year following birth and (ii) clinical severity of the depressive episode is linked to specific genetic variations [28]. Finally, epidemiological studies have shown an association between gene polymorphisms involved in stress regulation and mood disorders/PND [28, 29].

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Socio-economic and psychological factors are also of great importance in the risk of developing PND. Social context can be either protective (i.e. social support) or deleterious (i.e. low income), and thus responsible of stress levels during pregnancy [30]. Epidemiological studies show a link between maternal anxiety and mood symptoms during pregnancy and PND [31]. Personality aspects (such as neuroticism and low self-esteem)[32], as well as coping strategies [33], appear to be key factors in PND vulnerability.

Mindfulness is a psychological quality that involves bringing one's complete attention to the present experience on a moment-to-moment basis and in a particular way: in the present moment, and nonjudgmentally [34]. This ability is associated with low neuroticism, high self-esteem and efficient coping [35]. In both healthy individuals and people with medical conditions, mindfulness allows a better regulation of physiological and psychological stress [36, 37]. To the best of our knowledge, mindfulness and major maternal depressive episodes have never been studied. Since this ability is highly beneficial in preventing the development and relapse of depression, [38] one might expect PND to be less frequent in mindful women.

In light of the evidence gathered (biological, genetic and psychosocial), a hypothesis can be made: the risk of emergence of PND relies on an interaction between a maternal psychobiological vulnerability and a chronic environmental context of stress. PND appears as a relevant model for studying the mechanisms of chronic stress and vulnerability to psychological pathologies.

On the one hand, daily stressors (such as social, familial or work stress) during pregnancy correspond to a natural chronic stress model of several months and thus allows the study of the biological cost of responses to repeated stresses and the adaptive mechanisms leading to the functional drift to psychic dysfunction.

On the other hand, isolated vulnerability factors characterize a mirroring psychological profile of a Mindfulness type of functioning. This psychological resource has been associated with resistant or even resilient psychic functioning.

This study aims to follow a cohort of pregnant women from the first trimester of pregnancy to 12 months after delivery to determine the predictive psychobiological factors of the emergence of postnatal depression.

Objectives

The primary aim of the study is to determine the predictive psychobiological factors for the emergence of PND. It involves a multidisciplinary approach that will encompass psychological resources and biophysiological and genetic profiles.

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The secondary aims are to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We will follow changes in biological, physiological and psychological parameters in order to order to detect relevant vulnerability biomarkers for chronic stress and the development of PND.

Finally, two exploratory objectives will aim to assess the relevance of neurotrophic factors and genetic polymorphisms in the risk of developing PND.

Methods

Patient and public involvement

Patients and public were not involved in the development of the research question or in the design of the study. Dissemination of the general results (no personal data) would be made on demand.

Trial design and setting

We aim to undertake a multicentric prospective longitudinal study. The study will take place in hospitals where participants can be included in their first trimester of pregnancy. So far, 5 hospitals will be involved: Pôle HFME, CHR Mercy, Metz - Maternité GH Diaconesses Croix St Simon, Paris - Centre Aliénor d'Aquitaine, CHU Pellegrin, Bordeaux and Unité FIV, Pôle gynécologie, obstétrique et reproduction, CHU Estaing**,** Clermont-Ferrand – Centre Hospitalier Sud Francilien, CHSF Evry.

Eligibility criteria

The women involved in the study will have to meet the following requirements:

Inclusion criteria

- Before 17 weeks of gestation
- Pregnancy monitoring planned within one of the facilities involved in the project
- Full fluent in French
- Women over 18 years old
- Covered by the French National Health Service

Non-inclusion criteria

- Pathological pregnancy requiring increased medical monitoring
- Multiple pregnancy

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- Ongoing pathologies at the time of inclusion: (i) immune or endocrine conditions; (ii) any psychological disorders (PTSD, depression or anxiety disorders, etc.); or (iii) neurological pathologies such as multiple sclerosis.
- Hormonal or psychotropic drug therapies

End of the trial

During the study, if a participant meets one the following criteria, her participation will be discontinued:

- Withdrawal of consent
- Occurrence of a non-inclusion criteria
- Medical condition interfering with the protocol
- Death or "lost-to-follow-up"
- If a pregnancy becomes "pathological", the participant will have the choice to continue or to stop her involvement in the project; the pathological event will be reported in the case report form.

Recruitment started in April 2017 and will last 30 months.

Adverse events and other unintended effects of the study will be reported in compliance with the French public health code.

Intervention – participant timeline

This study aims to follow pregnant women, civilian or military, from the first trimester of pregnancy up to 12 months post-birth. As shown in Table 1, each woman will have to attend 10 visits: 1 visit within the first fourteen weeks of pregnancy (inclusion visit – VI), 1 visit every month during the others two trimesters of pregnancy (VP5 to VP9), 1 visit within the 48 hours of the birth (VB1), and 3 visits 2, 6 and 12 months after delivery (VB2, VB3 and VB4, respectively).

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	1st trimester			2nd trimester			3rd trimester		
Month	1	2	3	4	5	6	7	8	9
Visit	VI	VP5		VP6	VP7		VP8	VP9	

Delivery

1	2	3	4	5	6	7	8	9	10	11	12
VB1	VB2						VB3				VB4

	PREGNANCY						***POST-BIRTH***			
	Inclusion Visit - VI	Monthly visit during trimester 2 and 3					Post-delivery follow-up visits			
		VP5	VP6	VP7	VP8	VP9	VB1	VB2	VB3	VB4
Notice – Consent Forms	X									
Genetic sample	X									
Heart Rate Variability	X	X	X	X	X	X				
Blood sample	X		X			X	X			
Hair sample	X						X			
Questionnaires booklet	X	X	X	X	X	X	X	X	X	X

Table 1: Synopsis of study design. (top) Study timeline for each participant and (bottom) details of visit requirements. Each participant will have to attend 10 visits from their 1st trimester of pregnancy until 12 months post-delivery. VI: inclusion visit, VP: pregnancy visits from the 5th month to the 9th month of pregnancy, VB: post-birth visits 48 hours, 2, 6 and 12 months post-delivery.

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The last three VB visits may be performed remotely. The follow-up includes genetic, biological, physiological and/or psychological parameters. During the inclusion visit, participants will receive information on the protocol, provided by competent person (medical doctor or midwife), sign the consent forms (one to participate in the study and one for the genetic analysis) and undergo a complete assessment which includes psychological questionnaires, measurement of heart rate variability (HRV), and the collection of genetic, hair and blood samples. For the remaining 2 trimesters of pregnancy, psychological assessments and HRV measurements will be performed monthly whereas blood sampling will only be done on VP6 and VP8. Within 48 hours of the delivery (VB1), blood and hair will be collected and questionnaires will be completed. The last 3 visits (VB2, VB3 and VB4) will only require the completion of the psychological questionnaires. Details of the psychological questionnaires and genetic analyses can be found in tables 2 and 3.

Outcomes

The primary outcome of the study is the identification of predictive psychobiological risks factors for development of PND. PND will be assessed using the Edinburgh Post Depression Scale - EPDS (with a screening cut off >11) [39]. The EPDS is a 10-item self-report questionnaire assessing the symptoms of depression and anxiety. The factors assessed will include psychopathological and positive psychological aspects (see table 2 for detail of the questionnaires used).

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		PREGNANCY		POST BIRTH	
		Inclusion visit	VP5 to VP9	VB1	VB2, VB3 & VB4
Pathological	Symptom Checklist 90	x			
	State-Trait Anxiety Inventory	x		x (state)	x (state)
	Edinburg Postnatal Depression Scale	x		x	x
	PTSD Checklist for DMS-5	x			x
	Profile of Mood Scale	x	x		
	Questionnaire to detect the risk of PND	x	x		
	Traumatic Event Scale			x	
	Peritraumatic Dissociative Experiences Questionnaire			x	
	Traumatic Delivery Impact			x	
	Maternal Self Esteem				x
Personality	Temperament and Character Inventory	x			
Positive Psychology	Freiburg Mindfulness Inventory	x			
	Warwick Edinburg Mental Well-Being Scale	x			
	Prenatal Antenatal Inventory	x	x		
	Multidimensional Scale of Perceived Social Support	x	x	x	x
	Labour Agentry Scale			x	
Visual Analogic Scale	Professional stress	x	x		
	Personal stress	x	x		
	Sleep quality	x	x		
	Delivery Anticipatory Stress	x	x		
	Medical staff support during delivery			x	

Table 2: Summary of psychological and psychopathological questionnaires.
PND: postnatal depression. VAS : Visual Analogic Scale. Three psychological aspects are be studied: personality, psychopathology and positive psychology. VAS aim to determine stress level.

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The secondary outcomes will contribute to the understanding of the stress mechanisms involved throughout the pregnancy:

(i) Biological stress: GABA, TBARS (thiobarbituric acid reactive substances, byproducts of lipid peroxydation), inflammatory cytokines, cortisol and the endobiogenic index.

(ii) Physiological stress: measurement of heart rate variability (HRV) to determine the activation of the autonomous nervous system.

(iii) Psychological stress: perceived stress, social support and life quality.

The exploratory objectives will include the study of genetic polymorphisms linked to stress vulnerability (see table 3) and central functioning (BDNF and 8 iso-prostaglandine F2a).

Genes		Function
BDNF	Brain-Derived Neurotrophic Factor	Neuronal growth factor linked to the development of psychopathologies (such as anxiety)
COMT	Catechol-O-Methyltransferase	Involved in stress regulation (catecholamine)
NPY	Neuropeptide Y	Role in stress response, circadian rhythms and cardiovascular functions
NR3C1	Glucocorticoid Receptor (GR)	GR transcription factor
NR3C2	Mineralocorticoid Receptor (MR)	MR transcription factor
FKBP5	FK506 Binding Protein 5	Gene encoding co-chaperone protein essential in GR signalling
SLC6A4	Sodium-Dependent Serotonin Transporter	Serotonin transporter gene
NPS	Neuropeptide S	Peptide involves in anxiety, food intake and sleep quality.
NPSR1	Neuropeptide S Receptor	Receptor involves in anxiety, food intake and sleep quality.
CRHR1	Corticotropin Releasing Hormone Receptor	Involved in HPA axis regulation
DRD2	Dopamine Receptor D2	G protein-coupled receptor
OXT	Oxytocin/Neurophysin I Prepropeptide	Role in cognition, maternal behavior and cardiovascular functions
HMNCN1	Hemicentin-1	Protein involved in postpartum depression

Table 3: Summary of gene polymorphism analysis.
The chosen SNP aim to characterize vulnerability and severity of PND as well as stress sensitivity.

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Material

Heart Rate Variability: HRV will be measured in order to assess the reactivity of the autonomic nervous system (ANS). HRV will be recorded on a monthly basis using the CODESNA Physioner system. Heart rate, HRV components (high frequency, HF; low frequency, LF, and LF/HF ratio) will be examined as described by the Task Force.[40] The measurement of HRV will be conducted in sitting and resting participant.

Questionnaires: The psychological assessment will encompass pathological, personality, and positive psychology aspects (for details see table 2). Stress levels will be assessed using visual analogic scales. All the selected questionnaires are self-reporting questionnaires that have been validated in French and have demonstrated good psychometric properties. Ideally, all of these assessments should be performed before any potentially stressful exam.

Blood, hair and genetic samples: All sampling will be conducted according to the standard operating procedures described by the sponsor and in accordance with local procedures. Hair, blood and genetic samples will be conditioned locally and stored at room temperature or at -20°C. All biological materiel will then be transferred to the laboratories (Biolabs or IRBA) by a professional delivery company for analysis. Blood samples will be used for the analysis of all the biological parameters excepted of cortisol which will be assessed using hair.

Statistics

Number of participants needed

Several lines of evidence have been used in order to determine the number of participants required.

1/ Maternity activities: over 2 500 births/year in the CHU Pellegrin and CHR Mercy, 1 000 births/year in GH Diaconesses Croix St Simon and up to 200 medically-assisted procreations in the CHU Estaing.

2/ In the general population, prevalence of PND is 20%, therefore if we include 260 subjects, 52 should be diagnosed with PND. Among these, 5% of the mothers-to-be might discontinue the SERENE project before completion, so 42 participants with PND should remain.

3/ The psychometric tools used in the general population show that it is possible to distinguish between mindful and less mindful subjects within a sample of 20 subjects (Friburg Mindful Inventory cut-off score above 37). However, since mindfulness has never been assessed in pregnant women, no threshold between high and low mindfulness has been determined in such a population.

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4/ Given the prevalence of stress in the general population (30%), we expect to get 78 stressed subjects among the 260 participants included.

Therefore, we aim to recruit 260 participants, which represents less than 5% of the total pregnancies followed in the 5 centers in one year.

General design

Central tendency and the variability of the continuous variables will be described depending on whether or not they follow a normal distribution (using the Shapiro-Wilk test). If there is normal distribution, data will be summarized using means and standard deviations, if not medians and ranges will be used. VAS variables will be analyzed like ordinal data and described as above.

If required, class gathering into categorical variables will be performed. These variables will be described as absolute values and percentages.

Any variable with more than 10% missing data will not be analyzed.

Analyses for the primary outcome

A cut-off score of 11 in the EPDS has been shown to be a sensitive and specific threshold for PND emergence. We will use multivariate logistic regression in order to detect predictive factors of PND emergence. Threshold sensitivity in terms of sensitivity, specificity and predictive value will be performed using Receiver Operating Characteristic (ROC) analysis.

A two-step approach will be conducted. Firstly, a theme reasoned mixed approach will be undertaken to evaluate the weight of each biomarker for PND risk. 4 themes have been identified: (i) biography (full-term delivery, life events), (ii) psychological resources, (iii) biophysiological profiles and (iv) genetics. A final model will then be determined using mixed logistic regression from the variables selected from the previous step.

Analyses for the secondary and exploratory outcomes

The role of each biomarker and psychological factor in PND will be compared between the 2 groups (PND and non-PND) using an ANOVA factorial analysis. Life events during the pregnancy and the subject's status (civilian, military or spouse of force personnel) will be considered. PND risk factors linked to difficult labour/delivery will be controlled.

Finally, a composite index taking all the relevant biomarkers together will be computed in order to have a single predictive variable for the risk of developing PND.

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Data collection and management

In order to ensure the quality of the data collected and to promote participant retention, an assistant will be in charge of conducting the project according to the protocol in each centre involved in the SERENE project. The study will be implemented and conducted by the CRA coordinator of the DCSSA in accordance with to the monitoring plan. As much as possible, the CRA will ensure the quality of the collected data in each center in order to minimize missing data.

Personal information, data entry, coding, security and storage are processed in compliance with the Data Processing, Data Files and Individual Liberties Act of 6 January 1978.

Ethics and dissemination

Ethical approval has been obtained from the Ile de France III Ethics Committee (Hopital Tarnier-Cochin, Paris), France (2016-A00887-44). The study poses little to no risk to the participants or their infants, and does not interfere with the typical care received during pregnancy. This protocol will certainly detect some episodes of depression; such an event will be communicated to the caregivers or the participant herself in order to set up an adequate alternative care. Study results will be disseminated at national and international conferences and in peer-reviewed journals. The trial findings could also be made available to participants collectively. Any modifications of the protocol will be submitted to the competent authorities (if required) and communicated to every relevant party as specified by the French public health code.

All the data will remain the property of the sponsor. The final data report will be written by all the associated scientific investigators (as defined in the protocol).

Discussion

Potential limitations

We have identified two potential limitations:

(i) Given the way none pathological pregnancies are medically monitored in France (mostly outside of hospitals until the last 2 months of pregnancy) it may be difficult to include 260 participants in their first trimester. For this reason a "recruiting network" was initiated in each maternity (i.e. involvement of doctors doing first trimester ultrasounds, network of independent midwives) which should help to reach this goal.

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(ii) For the study, participants need to attend 10 visits, which might seem demanding. Furthermore, the last three visits are important since the diagnosis of PND may be made at this time. So, to make sure that participants will complete the protocol, one person (other than the investigators) is in charge of the participants' follow-up in each maternity.

Trial status

The study is currently recruiting participants.

Abbreviations

ANS : Autonomic Nervous System

ACTH**:** Adreno Cortico Trophine Hormone

BDNF: Brain-Derived Neurotrophic Factor

CRH: Corticotropin Releasing Hormone

EPDS: Edinburgh Postnatal Depression Scale

GABA: γ-aminobutyric acid

HPA axis: Hypothalamo-Pituitary-Adrenal axis

HRV: Heart Rate Variability

PND: PostNatal Depression

PTSD: Post Traumatic Stress Disorder

TBARS: Thiobarbituric Acid Reactive Substances

Contributors

MT, DT, and AD were involved in the conception and design of the trial. They also wrote the draft of the article. ASD, DD, ES, TH, EW, JLP and FD contributed to the refinement of the study protocol and provided expert insight. MT, DF, AD were responsible for the ethics committee. FC, MB, LC, FT carried out the study in the different maternities. All the authors were involved in final approval of the manuscript.

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Roles and responsibilities

The study sponsor is the Direction centrale du service de santé des armées (DCSSA - Fort neuf de Vincennes, Cours des maréchaux, 75 614 Paris Cedex 12). The coordinator, clinical

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research associate coordinator and the "Bureau de gestion de la recherche clinique" are in charge of the study logistics: quality of the data collected in the CRF, creation of input masks, computerization and quality control of the data. Since the study does not involve the use of product or medication, and only represents minor risks and constraints, no data monitoring committee has been formed.

Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Since the manuscript is a protocol paper there is no unpublished data. The original protocol (version 2 – 25.07.2016) for this study is available by contacting the corresponding author via email.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 12
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____4 onwards
	6b	Explanation for choice of comparators	_____NA_____
Objectives	7	Specific objectives or hypotheses	_____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____ 9 & 11___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8 & Figure 1__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files 1 & 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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BMJ Open

Chronic stress protection for postnatal dEpREssioN prEvention (SERENE): a protocol for an exploratory study

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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Complementary medicine
Keywords:	postnatal depression,, stress, mindfulness, allostatic load

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Chronic Stress protection for postnatal dEpREssioN prevention (SERENE): a protocol for an exploratory study

Tharwat Dahlia[1], Trousselard Marion[2], Balès Melanie[3], Sutter-Dallay Anne-Laure[3], Fromage Dominique[2], Spitz Elisabeth[4], Dallay Dominique[5], Harvey Thierry[1], Welter Eric[6], Coatleven Frédéric [5], Cherier Lydie[5], Teissedre Frédérique[7], Pouly Jean-Luc[8], Dutheil Frédéric[9], Duffaud Anaïs M.[2]

[1] Maternité GH Diaconesses Croix St Simon, F-75012 Paris, France

[2]Unité de Neurophysiologie du Stress, Département Neurosciences et Contraintes Opérationnelles, Institute de Recherche Biomédicale des Armées, F-91223 Brétigny-sur-Orge Cedex, France

[3] INSERM 1219, EPS Charles Perrens et Centre de Recherche, F-33000 Bordeaux, France

[4] University of Lorraine, Apemac, avenue de la Foret de Haye, F-54500 Vandœuvre-lès-Nancy, France

[5] CHU Pellegrin, University Hospital of Bordeaux, Centre Aliénor d'Aquitaine, F-33000 Bordeaux, France

[6] CHR Mercy, Regional Hospital of Metz, Pôle HFME, F-57000 Metz, France

[7] CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Department of In-Vitro Fecondation, Gynecologia, F-63000 Clermont-Ferrand, France

[8] Université Clermont Auvergne, UMR CNRS 6024, LaPSCo, Physiological and Psychosocial Stress, CHU Clermont-Ferrand, University Hospital of Clermont-Ferrand, Occupational and Preventive Medicine, WittyFit, F-63000 Clermont-Ferrand, France

[9] Australian Catholic University, Faculty of Health, Melbourne, Victoria 3065, Australia

* Correspondences to: Anaïs Duffaud; anaisduffaud1@gmail.com

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Abstract

Introduction: The prevalence of postnatal depression (PND) is significant: reaching up to 20% in a the general population. In mechanistic terms, the risk of PND lies in an interaction between a maternal psychophysiological vulnerability and a chronic environmental context of stress. On the one hand, repetition of stressor during pregnancy mimics a chronic stress model that is relevant to the study of the allostatic load and the adaptive mechanisms. On the other hand, vulnerability factors reflect a psychological profile mirroring Mindfulness functioning (psychological quality that involves bringing one's complete and nonjudgmental attention to the present experience on a moment-to-moment basis). This psychological resource is linked to protective and resilient psychic functioning. Thus, PND appears to be a relevant model for studying the mechanisms of chronic stress and vulnerability to psychopathologies.

In this article, we present the protocol of an ongoing study (started in May 2017).

Methods and analysis: The study is being carried out in 5 maternities and will involve 260 women. We aim to determine the predictive psychobiological factors for PND emergence and to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We use a multidisciplinary approach that encompasses psychological resources and biophysiological and genetic profiles in order to detect relevant vulnerability biomarkers for chronic stress and the development of PND. To do so, each woman will be involved in the study from her first trimester of pregnancy until 12 months post-delivery.

Ethics and dissemination: Ethics approval was obtained from the Ile de France III Ethics Committee, France (2016-A00887-44). We aim to disseminate the findings through international conferences and international peer-reviewed journals.

Trial registration: Clinical Trials identifier NCT03088319

Keywords: postnatal depression, stress, mindfulness, allostatic load

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Strengths and limitations of this study

- Multidisciplinary approach to postpartum depression: genetic, physiological and psychosocial with 3 time points: 1, 6 and 12 months post-delivery.
- Identification of early-biomarkers that will be good predictors of postpartum depression in order to set up prophylactic intervention.
- Given the way none pathological pregnancies are medically monitored in France (mostly outside of hospitals until the last 2 months of pregnancy) it may be difficult to include 260 participants in their first trimester.

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Background

Mounting evidence shows that the perinatal period is a time of increased vulnerability for mood disturbances and the onset of psychiatric disorders [1, 2]. Among puerperal disorders, baby blues, postnatal depression (PND) and puerperal psychosis are the most frequent [1]. While baby blues appears to be a normal adaptive phenomenon, PND and puerperal psychosis are psychopathologies associated with maternal suffering and have negative consequences for the offspring and the family. PND, the most common childbearing complication, has a prevalence range of 10 to 20% in western countries [2, 3]. It is described as a non-psychotic depressive episode of mild to moderate severity, beginning in or extending into the first postnatal year [4]. In the literature, two postpartum peaks have been identified: 4 weeks and 6 months post-delivery [5, 6]. It is also important to note that PND is the first episode of depression in 6 out of 10 women [7].

There is no specific diagnostic classification of PND. However, signs and symptoms are described in the DSM V as being similar to those observed in major depressive episodes but with a peripartum onset specifier (either before or after childbirth) [8-10]. Therefore, the symptoms profile of PND is characterized by major negative effects that are associated with anhedonia (loss of interest in pleasurable activities) and aboulia (e.g. behavioral disruption of sleep, appetite, etc.) [7]. Such symptoms have to be observed for a minimum of 2 weeks and must represent a change from the previous functioning. PND has significant impact on the mother, her partner, the family, mother-infant interactions and on the long-term emotional and cognitive development of the baby. Besides being used for clinical diagnosis, the Edinburgh Postnatal Depression Scale (EPDS) is a screening tool widely used to detect and assess the severity of the depression [11].

During pregnancy and postpartum periods, the maternal organism undergoes remarkable biological, physical, social and emotional changes. The most studied biological mechanisms are neuroendocrine abnormalities. The hormone withdrawal hypothesis of PND is supported by a number of human and non-human studies: the onset of depressive symptoms is linked to the sudden drop in the concentration of ovarian hormones (estradiol and progesterone) [12, 13]. Hypothalamo-pituitary-adrenal axis (HPA axis) dysfunction also seems to be implicated in PND onset. Corticotropin Releasing Hormone (CRH), Adreno Cortico Trophine Hormone (ACTH) and cortisol levels increase during pregnancy and up to a few days post-delivery and then normalize within 12 weeks post childbirth [14, 15]. Conversely, the involvement of thyroid function in the mother's major depressive episode remains unclear [13].

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Recent neurobiological studies have provided evidence for the involvement of the emotional neuronal circuit in this psychopathology [16, 17]. GABA (γ-aminobutyric acid) is a potent inhibitory neurotransmitter that has been shown to be altered in PND (decreased inhibition), mainly due to altered receptor functionality [18]. It is worth noting that GABA functioning is highly dependent upon the oxidative status, which is a consequence of an imbalance between the production of free radicals and the failure of the antioxidant defense mechanisms. This dysregulation has been observed in psychopathological disorders such a depression [19].

Furthermore, three stress-modulator neurotransmitters seem to be directly or indirectly involved in PND: serotonin, dopamine and oxytocin [20][21]. Chronic stress induces metabolic drift associated with reduced serotoninergic and dopaminergic transmission, and is probably linked to inflammation as well as depression [20]. The deleterious effects of stressful situations during the postpartum period (up to 9 weeks) are buffered by endogenous oxytocin, thus protecting women from developing depression [22].

Other than its unique function during pregnancy, brain-derived neurotrophic factor (BDNF) is a key mediator in neuronal plasticity and in mental disorders such as depression [23]. The neurotrophin hypothesis argues that a stress-induced decrease of BDNF is linked with aberrant neurogenesis and subsequent major depression. This decreased BDNF activity in the brain is correlated with serum/plasma BDNF concentration. Low serum BDNF in late pregnancy is associated with higher depressive symptoms [24].

In addition to hormonal and stress systems, immune dysregulation has also been hypothesized to contribute to PND. While pro-inflammatory cytokines decrease during pregnancy, anti-inflammatory cytokines increase. Within the first few hours after delivery, a sudden shift occurs that leads to the installation of a pro-inflammatory state [25]. The role of the immune function in the pathophysiology of depression is now clear : higher levels of pro-inflammatory cytokines are associated with depressive episodes [26].

Vulnerability to develop PND also arises from genetic polymorphism [27]. Several lines of evidence suggest that (i) there is a specific genetic polymorphism of major depressive episodes occurring in the first year following birth and (ii) clinical severity of the depressive episode is linked to specific genetic variations [28]. Finally, epidemiological studies have shown an association between gene polymorphisms involved in stress regulation and mood disorders/PND [28, 29].

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Socio-economic and psychological factors are also of great importance in the risk of developing PND. Social context can be either protective (i.e. social support) or deleterious (i.e. low income), and thus responsible of stress levels during pregnancy [30]. Epidemiological studies show a link between maternal anxiety and mood symptoms during pregnancy and PND [31]. Personality aspects (such as neuroticism and low self-esteem)[32], as well as coping strategies [33], appear to be key factors in PND vulnerability.

Mindfulness is a psychological quality that involves bringing one's complete attention to the present experience on a moment-to-moment basis and in a particular way: in the present moment, and nonjudgmentally [34]. This ability is associated with low neuroticism, high self-esteem and efficient coping [35]. In both healthy individuals and people with medical conditions, mindfulness allows a better regulation of physiological and psychological stress [36, 37]. To the best of our knowledge, mindfulness and major maternal depressive episodes have never been studied. Since this ability is highly beneficial in preventing the development and relapse of depression, [38] one might expect PND to be less frequent in mindful women.

In light of the evidence gathered (biological, genetic and psychosocial), a hypothesis can be made: the risk of emergence of PND relies on an interaction between a maternal psychobiological vulnerability and a chronic environmental context of stress. PND appears as a relevant model for studying the mechanisms of chronic stress and vulnerability to psychological pathologies.

On the one hand, daily stressors (such as social, familial or work stress) during pregnancy correspond to a natural chronic stress model of several months and thus allows the study of the biological cost of responses to repeated stresses and the adaptive mechanisms leading to the functional drift to psychic dysfunction.

On the other hand, isolated vulnerability factors characterize a mirroring psychological profile of a Mindfulness type of functioning. This psychological resource has been associated with resistant or even resilient psychic functioning.

This study aims to follow a cohort of pregnant women from the first trimester of pregnancy to 12 months after delivery to determine the predictive psychobiological factors of the emergence of postnatal depression.

Objectives

The primary aim of the study is to determine the predictive psychobiological factors for the emergence of PND. It involves a multidisciplinary approach that will encompass psychological resources and biophysiological and genetic profiles.

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The secondary aims are to provide a better insight into the mechanisms involved in chronic stress during pregnancy. We will follow changes in biological, physiological and psychological parameters in order to order to detect relevant vulnerability biomarkers for chronic stress and the development of PND.

Finally, two exploratory objectives will aim to assess the relevance of neurotrophic factors and genetic polymorphisms in the risk of developing PND.

Methods

Patient and public involvement

Patients and public were not involved in the development of the research question or in the design of the study. Dissemination of the general results (no personal data) would be made on demand.

Trial design and setting

We aim to undertake a multicentric prospective longitudinal study. The study will take place in hospitals where participants can be included in their first trimester of pregnancy. So far, 5 hospitals will be involved: Pôle HFME, CHR Mercy, Metz - Maternité GH Diaconesses Croix St Simon, Paris - Centre Aliénor d'Aquitaine, CHU Pellegrin, Bordeaux and Unité FIV, Pôle gynécologie, obstétrique et reproduction, CHU Estaing**,** Clermont-Ferrand – Centre Hospitalier Sud Francilien, CHSF Evry.

Eligibility criteria

The women involved in the study will have to meet the following requirements:

Inclusion criteria

- Before 17 weeks of gestation
- Pregnancy monitoring planned within one of the facilities involved in the project
- Full fluent in French
- Women over 18 years old
- Covered by the French National Health Service

Non-inclusion criteria

- Pathological pregnancy requiring increased medical monitoring
- Multiple pregnancy

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- Ongoing pathologies at the time of inclusion: (i) immune or endocrine conditions; (ii) any psychological disorders (PTSD, depression or anxiety disorders, etc.); or (iii) neurological pathologies such as multiple sclerosis.
- Hormonal or psychotropic drug therapies

End of the trial

During the study, if a participant meets one the following criteria, her participation will be discontinued:

- Withdrawal of consent
- Occurrence of a non-inclusion criteria
- Medical condition interfering with the protocol
- Death or "lost-to-follow-up"
- If a pregnancy becomes "pathological", the participant will have the choice to continue or to stop her involvement in the project; the pathological event will be reported in the case report form.

Recruitment started in April 2017 and will last 30 months.

Adverse events and other unintended effects of the study will be reported in compliance with the French public health code.

Intervention – participant timeline

This study aims to follow pregnant women, civilian or military, from the first trimester of pregnancy up to 12 months post-birth. As shown in Table 1, each woman will have to attend 10 visits: 1 visit within the first fourteen weeks of pregnancy (inclusion visit – VI), 1 visit every month during the others two trimesters of pregnancy (VP5 to VP9), 1 visit within the 48 hours of the birth (VB1), and 3 visits 2, 6 and 12 months after delivery (VB2, VB3 and VB4, respectively).

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	1st trimester			2nd trimester			3rd trimester		
Month	1	2	3	4	5	6	7	8	9

Delivery	1	2	3	4	5	6	7	8	9	10	11	12

Visit	VI	VP5	VP6	VP7	VP8	VP9	VB1	VB2				VB3				VB4

	PREGNANCY						***POST-BIRTH***			
	Inclusion Visit - VI	Monthly visit during trimester 2 and 3					Post-delivery follow-up visits			
		VP5	VP6	VP7	VP8	VP9	VB1	VB2	VB3	VB4
Notice – Consent Forms	X									
Genetic sample	X									
Heart Rate Variability	X	X	X	X	X	X				
Blood sample	X		X			X	X			
Hair sample	X						X			
Questionnaires booklet	X	X	X	X	X	X	X	X	X	X

Table 1: Synopsis of study design. (top) Study timeline for each participant and (bottom) details of visit requirements. Each participant will have to attend 10 visits from their 1st trimester of pregnancy until 12 months post-delivery. VI: inclusion visit, VP: pregnancy visits from the 5th month to the 9th month of pregnancy, VB: post-birth visits 48 hours, 2, 6 and 12 months post-delivery.

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The last three VB visits may be performed remotely. The follow-up includes genetic, biological, physiological and/or psychological parameters. During the inclusion visit, participants will receive information on the protocol, provided by competent person (medical doctor or midwife), sign the consent forms (one to participate in the study and one for the genetic analysis) and undergo a complete assessment which includes psychological questionnaires, measurement of heart rate variability (HRV), and the collection of genetic, hair and blood samples. For the remaining 2 trimesters of pregnancy, psychological assessments and HRV measurements will be performed monthly whereas blood sampling will only be done on VP6 and VP8. Within 48 hours of the delivery (VB1), blood and hair will be collected and questionnaires will be completed. The last 3 visits (VB2, VB3 and VB4) will only require the completion of the psychological questionnaires. Details of the psychological questionnaires and genetic analyses can be found in tables 2 and 3.

Outcomes

The primary outcome of the study is the identification of predictive psychobiological risks factors for development of PND. PND will be assessed using the Edinburgh Post Depression Scale - EPDS (with a screening cut off >11) [39]. The EPDS is a 10-item self-report questionnaire assessing the symptoms of depression and anxiety. The factors assessed will include psychopathological and positive psychological aspects (see table 2 for detail of the questionnaires used).

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		PREGNANCY		POST BIRTH	
		Inclusion visit	VP5 to VP9	VB1	VB2, VB3 & VB4
Pathological	Symptom Checklist 90	x			
	State-Trait Anxiety Inventory	x		x (state)	x (state)
	Edinburg Postnatal Depression Scale	x		x	x
	PTSD Checklist for DMS-5	x			x
	Profile of Mood Scale	x	x		
	Questionnaire to detect the risk of PND	x	x		
	Traumatic Event Scale			x	
	Peritraumatic Dissociative Experiences Questionnaire			x	
	Traumatic Delivery Impact			x	
	Maternal Self Esteem				x
Personality	Temperament and Character Inventory	x			
Positive Psychology	Freiburg Mindfulness Inventory	x			
	Warwick Edinburg Mental Well-Being Scale	x			
	Prenatal Antenatal Inventory	x	x		
	Multidimensional Scale of Perceived Social Support	x	x	x	x
	Labour Agentry Scale			x	
Visual Analogic Scale	Professional stress	x	x		
	Personal stress	x	x		
	Sleep quality	x	x		
	Delivery Anticipatory Stress	x	x		
	Medical staff support during delivery			x	

Table 2: Summary of psychological and psychopathological questionnaires.
PND: postnatal depression. VAS : Visual Analogic Scale. Three psychological aspects are be studied: personality, psychopathology and positive psychology. VAS aim to determine stress level.

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The secondary outcomes will contribute to the understanding of the stress mechanisms involved throughout the pregnancy:

(i) Biological stress: GABA, TBARS (thiobarbituric acid reactive substances, byproducts of lipid peroxydation), inflammatory cytokines, cortisol and the endobiogenic index.

(ii) Physiological stress: measurement of heart rate variability (HRV) to determine the activation of the autonomous nervous system.

(iii) Psychological stress: perceived stress, social support and life quality.

The exploratory objectives will include the study of genetic polymorphisms linked to stress vulnerability (see table 3) and central functioning (BDNF and 8 iso-prostaglandine F2a).

Genes		Function
BDNF	Brain-Derived Neurotrophic Factor	Neuronal growth factor linked to the development of psychopathologies (such as anxiety)
COMT	Catechol-O-Methyltransferase	Involved in stress regulation (catecholamine)
NPY	Neuropeptide Y	Role in stress response, circadian rhythms and cardiovascular functions
NR3C1	Glucocorticoid Receptor (GR)	GR transcription factor
NR3C2	Mineralocorticoid Receptor (MR)	MR transcription factor
FKBP5	FK506 Binding Protein 5	Gene encoding co-chaperone protein essential in GR signalling
SLC6A4	Sodium-Dependent Serotonin Transporter	Serotonin transporter gene
NPS	Neuropeptide S	Peptide involves in anxiety, food intake and sleep quality.
NPSR1	Neuropeptide S Receptor	Receptor involves in anxiety, food intake and sleep quality.
CRHR1	Corticotropin Releasing Hormone Receptor	Involved in HPA axis regulation
DRD2	Dopamine Receptor D2	G protein-coupled receptor
OXT	Oxytocin/Neurophysin I Prepropeptide	Role in cognition, maternal behavior and cardiovascular functions
HMNCN1	Hemicentin-1	Protein involved in postpartum depression

Table 3: Summary of gene polymorphism analysis.
The chosen SNP aim to characterize vulnerability and severity of PND as well as stress sensitivity.

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Material

Heart Rate Variability: HRV will be measured in order to assess the reactivity of the autonomic nervous system (ANS). HRV will be recorded on a monthly basis using the CODESNA Physioner system. Heart rate, HRV components (high frequency, HF; low frequency, LF, and LF/HF ratio) will be examined as described by the Task Force.[40] The measurement of HRV will be conducted in sitting and resting participant.

Questionnaires: The psychological assessment will encompass pathological, personality, and positive psychology aspects (for details see table 2). Stress levels will be assessed using visual analogic scales. All the selected questionnaires are self-reporting questionnaires that have been validated in French and have demonstrated good psychometric properties. Ideally, all of these assessments should be performed before any potentially stressful exam.

Blood, hair and genetic samples: All sampling will be conducted according to the standard operating procedures described by the sponsor and in accordance with local procedures. Hair, blood and genetic samples will be conditioned locally and stored at room temperature or at -20°C. All biological materiel will then be transferred to the laboratories (Biolabs or IRBA) by a professional delivery company for analysis. Blood samples will be used for the analysis of all the biological parameters excepted of cortisol which will be assessed using hair.

Statistics

Number of participants needed

Several lines of evidence have been used in order to determine the number of participants required.

1/ Maternity activities: over 2 500 births/year in the CHU Pellegrin and CHR Mercy, 1 000 births/year in GH Diaconesses Croix St Simon and up to 200 medically-assisted procreations in the CHU Estaing.

2/ In the general population, prevalence of PND is 20%, therefore if we include 260 subjects, 52 should be diagnosed with PND. Among these, 5% of the mothers-to-be might discontinue the SERENE project before completion, so 42 participants with PND should remain.

3/ The psychometric tools used in the general population show that it is possible to distinguish between mindful and less mindful subjects within a sample of 20 subjects (Friburg Mindful Inventory cut-off score above 37). However, since mindfulness has never been assessed in pregnant women, no threshold between high and low mindfulness has been determined in such a population.

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4/ Given the prevalence of stress in the general population (30%), we expect to get 78 stressed subjects among the 260 participants included.

Therefore, we aim to recruit 260 participants, which represents less than 5% of the total pregnancies followed in the 5 centers in one year.

General design

Central tendency and the variability of the continuous variables will be described depending on whether or not they follow a normal distribution (using the Shapiro-Wilk test). If there is normal distribution, data will be summarized using means and standard deviations, if not medians and ranges will be used. VAS variables will be analyzed like ordinal data and described as above.

If required, class gathering into categorical variables will be performed. These variables will be described as absolute values and percentages.

Any variable with more than 10% missing data will not be analyzed.

Analyses for the primary outcome

A cut-off score of 11 in the EPDS has been shown to be a sensitive and specific threshold for PND emergence. We will use multivariate logistic regression in order to detect predictive factors of PND emergence. Threshold sensitivity in terms of sensitivity, specificity and predictive value will be performed using Receiver Operating Characteristic (ROC) analysis.

A two-step approach will be conducted. Firstly, a theme reasoned mixed approach will be undertaken to evaluate the weight of each biomarker for PND risk. 4 themes have been identified: (i) biography (full-term delivery, life events), (ii) psychological resources, (iii) biophysiological profiles and (iv) genetics. A final model will then be determined using mixed logistic regression from the variables selected from the previous step.

Analyses for the secondary and exploratory outcomes

The role of each biomarker and psychological factor in PND will be compared between the 2 groups (PND and non-PND) using an ANOVA factorial analysis. Life events during the pregnancy and the subject's status (civilian, military or spouse of force personnel) will be considered. PND risk factors linked to difficult labour/delivery will be controlled.

Finally, a composite index taking all the relevant biomarkers together will be computed in order to have a single predictive variable for the risk of developing PND.

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Data collection and management

In order to ensure the quality of the data collected and to promote participant retention, an assistant will be in charge of conducting the project according to the protocol in each centre involved in the SERENE project. The study will be implemented and conducted by the CRA coordinator of the DCSSA in accordance with to the monitoring plan. As much as possible, the CRA will ensure the quality of the collected data in each center in order to minimize missing data.

Personal information, data entry, coding, security and storage are processed in compliance with the Data Processing, Data Files and Individual Liberties Act of 6 January 1978.

Ethics and dissemination

Ethical approval has been obtained from the Ile de France III Ethics Committee (Hopital Tarnier-Cochin, Paris), France (2016-A00887-44). The study poses little to no risk to the participants or their infants, and does not interfere with the typical care received during pregnancy. This protocol will certainly detect some episodes of depression; such an event will be communicated to the caregivers or the participant herself in order to set up an adequate alternative care. Study results will be disseminated at national and international conferences and in peer-reviewed journals. The trial findings could also be made available to participants collectively. Any modifications of the protocol will be submitted to the competent authorities (if required) and communicated to every relevant party as specified by the French public health code.

All the data will remain the property of the sponsor. The final data report will be written by all the associated scientific investigators (as defined in the protocol).

Discussion

Potential limitations

We have identified two potential limitations:

(i) Given the way none pathological pregnancies are medically monitored in France (mostly outside of hospitals until the last 2 months of pregnancy) it may be difficult to include 260 participants in their first trimester. For this reason a "recruiting network" was initiated in each maternity (i.e. involvement of doctors doing first trimester ultrasounds, network of independent midwives) which should help to reach this goal.

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(ii) For the study, participants need to attend 10 visits, which might seem demanding. Furthermore, the last three visits are important since the diagnosis of PND may be made at this time. So, to make sure that participants will complete the protocol, one person (other than the investigators) is in charge of the participants' follow-up in each maternity.

Trial status

The study is currently recruiting participants.

Abbreviations

ANS : Autonomic Nervous System

ACTH**:** Adreno Cortico Trophine Hormone

BDNF: Brain-Derived Neurotrophic Factor

CRH: Corticotropin Releasing Hormone

EPDS: Edinburgh Postnatal Depression Scale

GABA: γ-aminobutyric acid

HPA axis: Hypothalamo-Pituitary-Adrenal axis

HRV: Heart Rate Variability

PND: PostNatal Depression

PTSD: Post Traumatic Stress Disorder

TBARS: Thiobarbituric Acid Reactive Substances

Contributors

MT, DT, and AD were involved in the conception and design of the trial. They also wrote the draft of the article. ASD, DD, ES, TH, EW, JLP and FD contributed to the refinement of the study protocol and provided expert insight. MT, DF, AD were responsible for the ethics committee. FC, MB, LC, FT carried out the study in the different maternities. All the authors were involved in final approval of the manuscript.

Funding

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Roles and responsibilities

The study sponsor is the Direction centrale du service de santé des armées (DCSSA - Fort neuf de Vincennes, Cours des maréchaux, 75 614 Paris Cedex 12). The coordinator, clinical

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research associate coordinator and the "Bureau de gestion de la recherche clinique" are in charge of the study logistics: quality of the data collected in the CRF, creation of input masks, computerization and quality control of the data. Since the study does not involve the use of product or medication, and only represents minor risks and constraints, no data monitoring committee has been formed.

Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Since the manuscript is a protocol paper there is no unpublished data. The original protocol (version 2 – 25.07.2016) for this study is available by contacting the corresponding author via email.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 12
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____4 onwards
	6b	Explanation for choice of comparators	_____NA_____
Objectives	7	Specific objectives or hypotheses	_____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____ 9 & 11___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____8_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_8 & Figure 1__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files 1 & 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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